

=> d his

(FILE 'HOME' ENTERED AT 19:14:22 ON 04 MAR 2011)

FILE 'REGISTRY' ENTERED AT 19:14:29 ON 04 MAR 2011

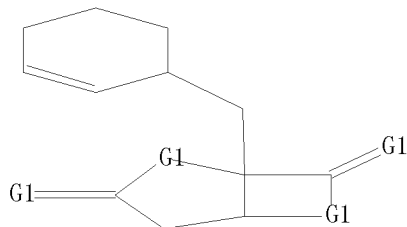
L1 STRUCTURE UPLOADED

L2 12 S L1

L3 276 S L1 FULL

=> d que l3 stat

L1 STR



G1 0, S, N

Structure attributes must be viewed using STN Express query preparation.

L3 276 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 3469 ITERATIONS

276 ANSWERS

SEARCH TIME: 00.00.01

=> s l3 and caplus/lc

73780714 CAPLUS/LC

L4 272 L3 AND CAPLUS/LC

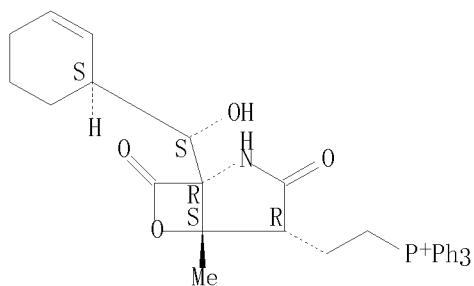
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L5 4 L3 NOT L4

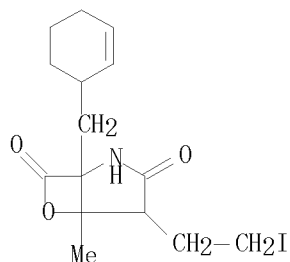
=> d 1-4 ide can

L5 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2011 ACS on STN  
RN 1067275-91-5 REGISTRY  
ED Entered STN: 28 Oct 2008  
CN Phosphonium, [2-[(1R,4R,5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl]triphenyl- (CA  
INDEX NAME)  
FS STEREOSEARCH  
MF C33 H35 N 04 P  
CI COM  
SR CA

Absolute stereochemistry.

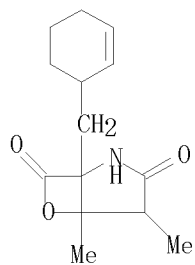


L5 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2011 ACS on STN  
RN 1026864-46-9 REGISTRY  
ED Entered STN: 10 Jun 2008  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(2-cyclohexen-1-ylmethyl)-4-(2-iodoethyl)-5-methyl- (CA INDEX NAME)  
MF C15 H20 I N O3  
SR Other Sources  
Database: ChemSpider (ChemZoo, Inc.)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

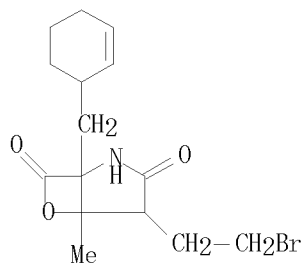
L5 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2011 ACS on STN  
RN 1026616-24-9 REGISTRY  
ED Entered STN: 08 Jun 2008  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(2-cyclohexen-1-ylmethyl)-4,5-dimethyl- (CA INDEX NAME)  
MF C14 H19 N O3  
SR Other Sources  
Database: ChemSpider (ChemZoo, Inc.)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*



L5 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2011 ACS on STN  
RN 1026453-56-4 REGISTRY  
ED Entered STN: 08 Jun 2008  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-(2-cyclohexen-1-ylmethyl)-5-methyl- (CA INDEX NAME)  
MF C15 H20 Br N O3  
SR Other Sources  
Database: ChemSpider (ChemZoo, Inc.)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

=> fil capl  
FILE 'CAPLUS' ENTERED AT 19:16:04 ON 04 MAR 2011  
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FILE COVERS 1907 - 4 Mar 2011 VOL 154 ISS 11  
FILE LAST UPDATED: 3 Mar 2011 (20110303/ED)  
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2010  
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2010

Caplus now includes complete International Patent Classification (IPC) reclassification data for the fourth quarter of 2010.

CAS Information Use Policies apply and are available at:

<http://www.cas.org/legal/infopolicy.html>

This file contains CAS Registry Numbers for easy and accurate substance identification.

'FIONA' IS DEFAULT FORMAT FOR 'CAPLUS' FILE

=> s l3  
L6 169 L3

=> d 1-169 ibib iabs hitstr

L6 ANSWER 1 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2011:108868 CAPLUS  
 DOCUMENT NUMBER: 154:199336  
 TITLE: Combination of proteasome inhibitors and  
 anti-hepatitis medication for treating hepatitis  
 INVENTOR(S): Schubert, Ulrich  
 PATENT ASSIGNEE(S): Virologik GmbH, Germany  
 SOURCE: PCT Int. Appl., 148pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

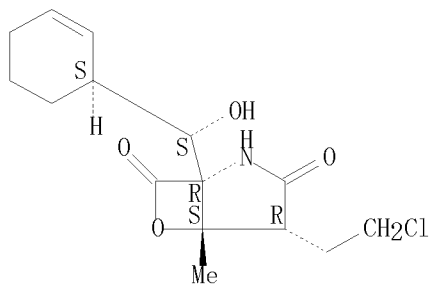
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2011009961	A1	20110127	WO 2010-EP60796	20100726
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
DE 102009028015	A1	20110127	DE 2009-102009028015	20090724
PRIORITY APPLN. INFO.:			DE 2009-102009028015A	20090724
			EP 2010-151135	A 20100119
			US 2010-296363P	P 20100119

## ABSTRACT:

The present invention relates to kit of pharmaceutical compns. for the treatment of a hepatitis viral infection in a human or animal individual who does not respond or is refractory to treatment with at least one pharmaceutically active agent in use against viral hepatitis infections, comprising: (a) at least one first pharmaceutical composition comprising at least one proteasome inhibitor; (b) at least one second pharmaceutical composition comprising at least one first different pharmaceutically active agent in use against viral hepatitis infections, and (c) optionally at least one second different pharmaceutically active agent in use against viral hepatitis infections, comprised in said at least one second or in at least one third pharmaceutical composition

IT 437742-34-2, Salinosporamide A  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combination of proteasome inhibitors and anti-hepatitis medication for treating hepatitis)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2010:1632261 CAPLUS  
 DOCUMENT NUMBER: 154:101765  
 TITLE: Materials and methods for treating and preventing  
 viral infections and cancer using peptide antagonists  
 of SOCS-1 or SOCS-3  
 INVENTOR(S): Johnson, Howard M.; Ahmed, Chulbul Iqbal M.  
 PATENT ASSIGNEE(S): University of Florida, USA  
 SOURCE: PCT Int. Appl., 110pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010151495	A2	20101229	WO 2010-US39195	20100618
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
PRIORITY APPLN. INFO.:			US 2009-220920P	P 20090626
			US 2010-354124P	P 20100611

## ABSTRACT:

The subject invention concerns materials and methods for inhibiting activity of a broad spectrum of viruses in humans and animals. In one embodiment of the invention, a method is provided for treating or preventing viral infection in an animal by administering an effective amount of peptide that is an antagonist of SOCS-1 and/or SOCS-3. In a specific embodiment, the peptide corresponds to the activation loop of janus kinase JAK2. In an exemplified embodiment, the peptide has the amino acid sequence: LPQDKKEYKVKPEP (pJAK2 (1001-1013)) (SEQ ID NO:1). Compns. contemplated within the scope of the invention include peptides of the invention and optionally one or more other antiviral compds. Examples of viruses whose replication can be inhibited using the present invention include, but are not limited to, vaccinia virus, EMC virus, influenza virus, and herpes simplex virus. In addition to treating a human or animal having a viral infection, the subject invention can also be used to prevent viral infection in an uninfected human or animal. The peptide, or polynucleotide encoding it, can also be used to treat cancer.

IT **437742-34-2**, Salinosporamide A

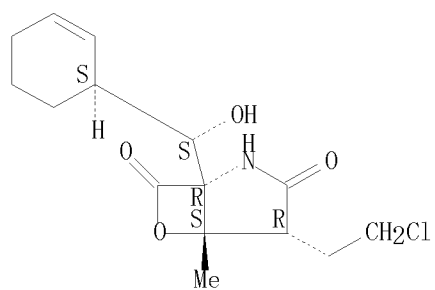
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(as further antitumor agent; materials and methods for treating and preventing viral infections using peptide antagonists of SOCS-1 or SOCS-3)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 3 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:1630416 CAPLUS  
DOCUMENT NUMBER: 154:83336  
TITLE: Materials and methods for the identification of  
drug-resistant cancers and treatment  
INVENTOR(S): Zhan, Fenghuang; Zangari, Maurizio; Tricot, Guido  
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA  
SOURCE: PCT Int. Appl., 67pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010151731	A1	20101229	WO 2010-US39927	20100625
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
PRIORITY APPLN. INFO.:			US 2009-269661P	P 20090626

## ABSTRACT:

Disclosed herein are diagnostic methods for identifying cancer and predicting drug resistance for cancer treatment. The assays involve the detection of NEK2 gene expression alone or in combination with other genes or clin. factors. The test is suitable for diagnosing and monitoring treatment of subjects having or suspected of having a neoplastic disease, such as multiple myeloma. The invention also relates to the use of inhibitors of NEK2 in the treatment of cancer, including drug-resistant multiple myeloma.

IT **437742-34-2**, Salinosporamide A

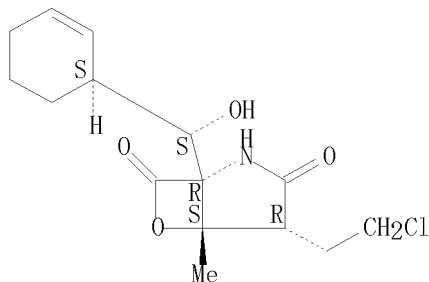
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(materials and methods for the identification of drug-resistant cancers and treatment)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



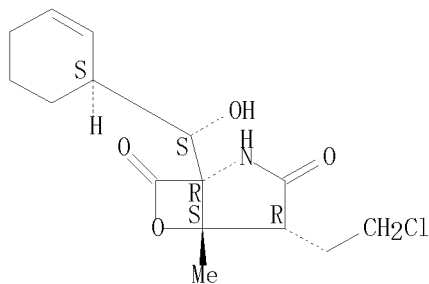
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:1614324 CAPLUS  
DOCUMENT NUMBER: 154:234347  
TITLE: Total Synthesis of (-)-Salinosporamide A  
AUTHOR(S): Kaiya, Yuji; Hasegawa, Jun-ichi; Momose, Takayuki;  
Sato, Takaaki; Chida, Noritaka  
CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Science  
and Technology, Keio University, 3-14-1, Hiyoshi,  
Kohoku-ku, Yokohama, 223-8522, Japan  
SOURCE: Chemistry—An Asian Journal (2011), 6(1), 209-219  
CODEN: CAAJBI; ISSN: 1861-4728  
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
ABSTRACT:

A detailed description of our second-generation total synthesis of salinosporamide A is presented. Three contiguous stereocenters in the  $\gamma$ -lactam structure seen in the natural product were established by stereoselective functionalization of a D-arabinose scaffold, including an Overman rearrangement to generate a highly congested tetrasubstituted carbon center. One of the definitive reactions in the synthesis was a Lewis acid mediated skeletal rearrangement of a pyranose structure, which enabled the practical conversion of the carbohydrate scaffold to the  $\gamma$ -lactam structure embedded in salinosporamide A. The use of a benzyl ester as a protective group for a sterically hindered carboxylic acid led to a one-pot global deprotection at the end of the synthesis.

IT **437742-34-2P**, (-)-Salinosporamide A  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(total synthesis of salinosporamide A via skeletal and Overman rearrangements)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

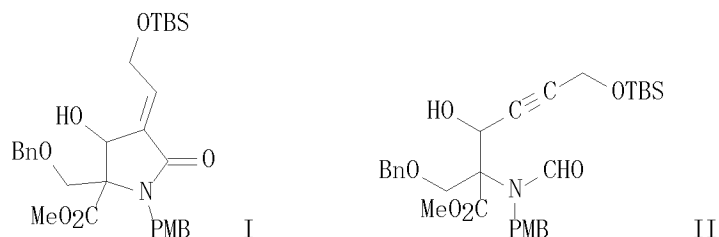
Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 130 THERE ARE 130 CITED REFERENCES AVAILABLE FOR  
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT



L6 ANSWER 5 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2010:1533193 CAPLUS  
 DOCUMENT NUMBER: 154:207305  
 TITLE: Synthetic studies of salinosporamide A through the  
 intramolecular hydroamidation of alkynes  
 AUTHOR(S): Kamisaki, Haruhi; Kobayashi, Yusuke; Kimachi,  
 Tetsutaro; Yasui, Yoshizumi; Takemoto, Yoshiji  
 CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Kyoto  
 University, Yoshida, Sakyo-ku, Kyoto, 606-8501, Japan  
 SOURCE: Journal of Organometallic Chemistry (2010), Volume  
 Date 2011, 696(1), 42-45  
 CODEN: JORCAI; ISSN: 0022-328X  
 PUBLISHER: Elsevier B.V.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GRAPHIC IMAGE:

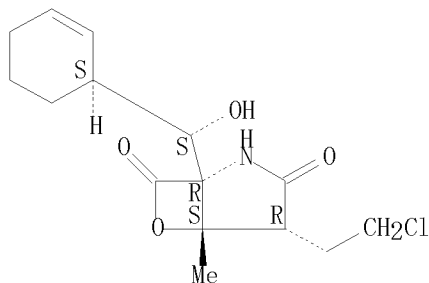


# ABSTRACT:

Rhodium-catalyzed intramol. hydroamidation of alkynes was carried out to construct the synthetic intermediates, e.g., I, of a proteasome inhibitor, salinosporamide A. Several alkynyl formamides, e.g., II, were synthesized and subjected to the hydroamidation reaction. Some derivs. with a methoxymethyl (MOM) or 2-methoxy-2-Pr (MOP) group near the reaction site were converted to the corresponding lactams in excellent yields.

IT **437742-34-2P**, (-)-Salinosporamide A  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (synthetic studies of salinosporamide A via intramol. hydroamidation of  
 alkynyl formamides)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



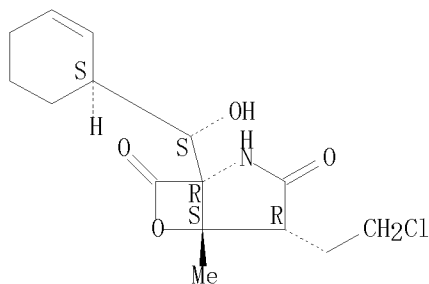
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:1506127 CAPLUS  
DOCUMENT NUMBER: 154:198281  
TITLE: Salinosporamide Natural Products: Potent 20S  
Proteasome Inhibitors as Promising Cancer  
Chemotherapeutics  
AUTHOR(S): Gulder, Tobias A. M.; Moore, Bradley S.  
CORPORATE SOURCE: Scripps Institution of Oceanography, Skaggs Sch.  
Pharm. Pharmaceutical Sci., Univ. California at San  
Diego, La Jolla, CA, 92093-0204, USA  
SOURCE: Angewandte Chemie, International Edition (2010),  
49(49), 9346-9367  
CODEN: ACIEF5; ISSN: 1433-7851  
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

A review. Proteasome inhibitors are rapidly evolving as potent treatment options in cancer therapy. One of the most promising drug candidates of this type is salinosporamide A from the bacterium *Salinispora tropica*. This marine natural product possesses a complex, densely functionalized  $\gamma$ -lactam- $\beta$ -lactone pharmacophore, which is responsible for its irreversible binding to its target, the  $\beta$  subunit of the 20S proteasome. Salinosporamide A entered phase I clin. trials for the treatment of multiple myeloma only three years after its discovery. The strong biol. activity and the challenging structure of this compound have fueled intense academic and industrial research in recent years, which has led to the development of more than ten syntheses, the elucidation of its biosynthetic pathway, and the generation of promising structure-activity relationships and oncol. data. Salinosporamide A thus serves as an intriguing example of the successful interplay of modern drug discovery and biomedical research, medicinal chemical and pharmacol., natural product synthesis and anal., as well as biosynthesis and bioengineering.

IT 437742-34-2, Salinosporamide A  
RL: NPO (Natural product occurrence); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses) (salinosporamide natural products as potent 20S proteasome inhibitors for cancer chemotherapeutics)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
(1 CITINGS)  
REFERENCE COUNT: 157 THERE ARE 157 CITED REFERENCES AVAILABLE FOR  
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L6 ANSWER 7 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2010:1382680 CAPLUS

DOCUMENT NUMBER: 154:30091

TITLE: Bioinspired Total Synthesis and Human Proteasome

Inhibitory Activity of (-)-Salinosporamide A,  
(-)-Homosalinosporamide A, and Derivatives Obtained  
via Organonucleophile Promoted Bis-cyclizations

AUTHOR(S): Nguyen, Henry; Ma, Gil; Gladysheva, Tatiana; Fremgen,  
Trisha; Romo, Daniel

CORPORATE SOURCE: Department of Chemistry, Texas A&M University, College  
Station, TX, 77842-3012, USA

SOURCE: Journal of Organic Chemistry (2011), 76(1), 2-12

CODEN: JOCEAH; ISSN: 0022-3263

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

ABSTRACT:

A full account of concise, enantioselective syntheses of the anticancer agent (-)-salinosporamide A and derivs., including (-)-homosalinosporamide, that was inspired by biosynthetic considerations is described. The brevity of the synthetic strategy stems from a key bis-cyclization of a  $\beta$ -keto tertiary amide, which retains optical purity enabled by A1,3-strain rendering slow epimerization relative to the rate of bis-cyclization. Optimization studies of the key bis-cyclization, enabled through byproduct isolation and characterization, are described that ultimately allowed for a gram scale synthesis of a versatile bicyclic core structure with a high degree of stereoretention. An optimized procedure for zincate generation by the method of Knochel, generally useful for the synthesis of salino A derivs., led to dramatic improvements in side-chain attachment and a novel diastereomer of salino A. The versatility of the described strategy is demonstrated by the synthesis of designed derivs. including (-)-homosalinosporamide A. Inhibition of the human 20S and 26S proteasome by these derivs. using an enzymic assay are also reported. The described total synthesis of salino A raises interesting questions regarding how biosynthetic enzymes leading to the salinosporamides proceeding via optically active  $\beta$ -keto secondary amides, are able to maintain the stereochem. integrity at the labile C2 stereocenter or if a dynamic kinetic resolution is operative.

IT 1256639-02-7P

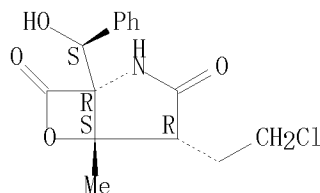
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(crystal structure; diastereo- and enantioselective preparation of (-)-salinosporamide A via bis-cyclization of  $\beta$ -keto tertiary amide in intramol. aldol/lactonization process and SAR of its proteasome inhibitory activity)

RN 1256639-02-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-hydroxyphenylmethyl]-5-methyl-, (1S,4S,5R)-rel-  
(CA INDEX NAME)

Relative stereochemistry.



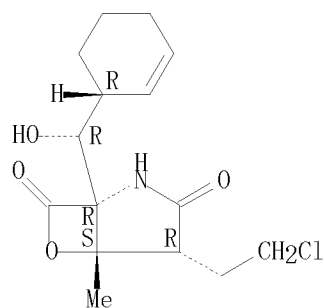
IT 1256842-57-5P

RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)  
(crystal structure; diastereo- and enantioselective preparation of (-)-salinosporamide A via bis-cyclization of  $\beta$ -keto tertiary amide in intramol. aldol/lactonization process and SAR of its proteasome inhibitory activity)

RN 1256842-57-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 942517-04-6P 942517-09-1P 1256638-99-9P  
1256639-01-6P 1256639-03-8P

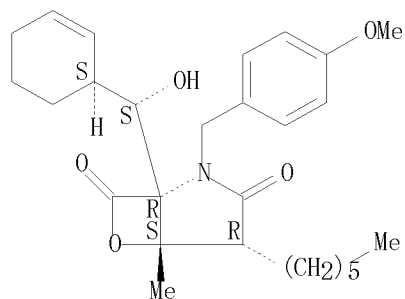
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(deprotection; diastereo- and enantioselective preparation of (-)-salinosporamide A via bis-cyclization of  $\beta$ -keto tertiary amide in intramol. aldol/lactonization process and SAR of its proteasome inhibitory activity)

RN 942517-04-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-2-[(4-methoxyphenyl)methyl]-5-methyl-, (1S,4S,5R)-rel- (CA INDEX NAME)

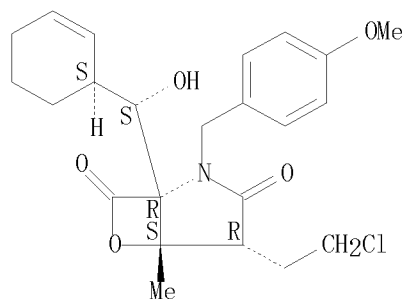
Relative stereochemistry.



RN 942517-09-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-2-[(4-methoxyphenyl)methyl]-5-methyl-, (1S,4S,5R)-rel- (CA INDEX NAME)

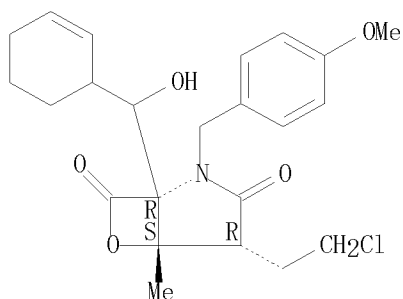
Relative stereochemistry.



RN 1256638-99-9 CAPLUS

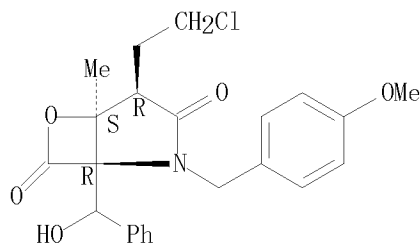
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-(2-cyclohexen-1-ylhydroxymethyl)-2-[(4-methoxyphenyl)methyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



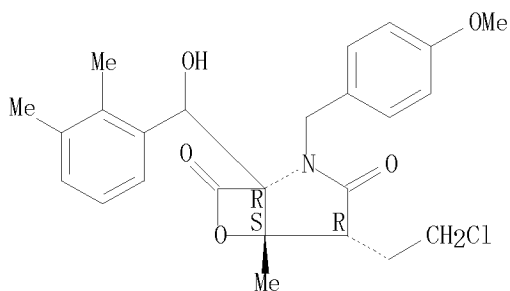
RN 1256639-01-6 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Relative stereochemistry.



RN 1256639-03-8 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

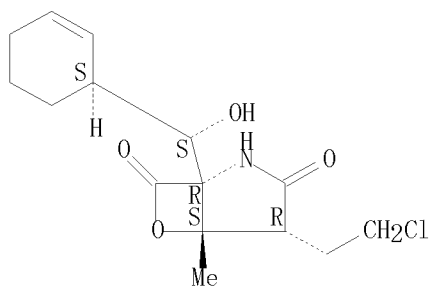
Relative stereochemistry.



IT **437742-34-2P**, (-)-Salinosporamide A  
RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(diastereo- and enantioselective preparation of (-)-salinosporamide A via bis-cyclization of  $\beta$ -keto tertiary amide in intramol. aldol/lactonization process and SAR of its proteasome inhibitory activity)

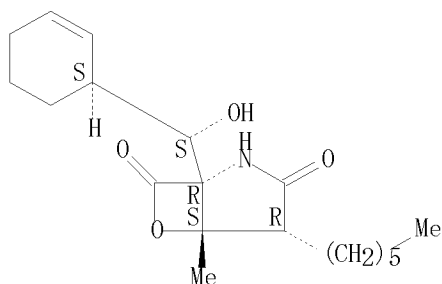
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



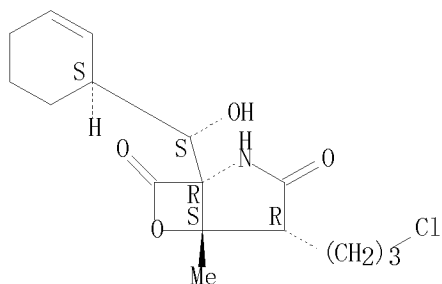
IT 942516-89-4P 1239987-24-6P, (-)-Homosalinosporamide  
 A 1256639-04-9P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
 (Uses)  
 (diastereo- and enantioselective preparation of (-)-salinosporamide A via  
 bis-cyclization of  $\beta$ -keto tertiary amide in intramol.  
 aldol/lactonization process and SAR of its proteasome inhibitory  
 activity)  
 RN 942516-89-4 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-,  
 (1S,4S,5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



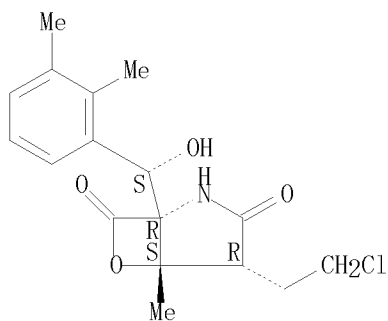
RN 1239987-24-6 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(3-chloropropyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 1256639-04-9 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-(2,3-dimethylphenyl)hydroxymethyl]-5-methyl-,  
 (1S,4S,5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



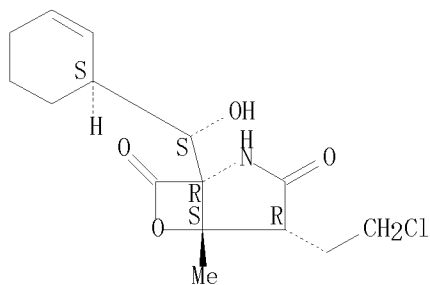
IT **909569-43-3P**

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (diastereo- and enantioselective preparation of (-)-salinosporamide A via  
 bis-cyclization of  $\beta$ -keto tertiary amide in intramol.  
 aldol/lactonization process and SAR of its proteasome inhibitory  
 activity)

RN 909569-43-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1S,4S,5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



OS.CITING REF COUNT:	1	THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT:	61	THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:1363281 CAPLUS  
TITLE: Bortezomib  
AUTHOR(S): Einsele, Hermann  
CORPORATE SOURCE: Department of Internal Medicine II, University  
Hospital Wuezburg, Wuerzburg, 97080, Germany  
SOURCE: Recent Results in Cancer Research (2010), 184(Small  
Molecules in Oncology), 173-187  
CODEN: RRCRBU; ISSN: 0080-0015  
PUBLISHER: Springer GmbH  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

The ubiquitin-mediated degradation of proteins in numerous cellular processes, such as turnover and quality control of proteins, cell cycle and apoptosis, transcription and cell signaling, immune response and antigen presentation, and inflammation and development makes the ubiquitin-proteasome systems a very interesting target for various therapeutic interventions. Proteasome inhibitors were first synthesized as tools to probe the function and specificity of this particle's proteolytic activities. Most synthetic inhibitors rely on a peptide base, which mimics a protein substrate, attached at a COOH terminal "warhead". Notable warheads include boronic acids, such as Bortezomib and epoxyketones, such as carfilzomib. A variety of natural products also inhibit the proteasome that are not peptide-based, most notably lactacystin, that is related to NPI-0052, or salinosporamide A, another inhibitor in clin. trials. The possibility that proteasome inhibitors could be drug candidates was considered after studies showed that they induced apoptosis in leukemic cell lines. The first proteasome inhibitor in clin. application, Bortezomib showed activity in non small cell lung and androgen-independent prostate carcinoma, as well as MM and mantle cell and follicular Non-Hodgkin's lymphoma. It is now licensed for the treatment of newly diagnosed as well as relapsed/progressive MM and has had a major impact on the improvement in the treatment of MM in the last few years.

IT INDEXING IN PROGRESS

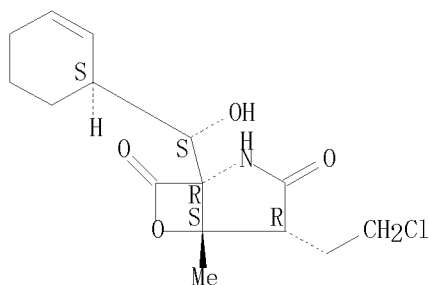
IT **437742-34-2**, Salinosporamide A

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(clin. application in proteasome inhibitor)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

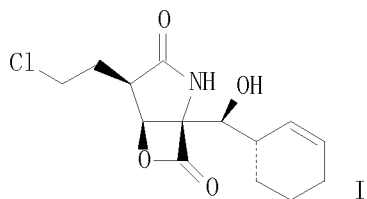


OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD  
(2 CITINGS)

REFERENCE COUNT: 154 THERE ARE 154 CITED REFERENCES AVAILABLE FOR  
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT



L6 ANSWER 9 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2010:1333311 CAPLUS  
 DOCUMENT NUMBER: 154:64491  
 TITLE: An enantio- and diastereocontrolled synthesis of  
 (-)-salinosporamide A  
 AUTHOR(S): Sato, Yosuke; Fukuda, Hayato; Tomizawa, Masaki;  
 Masaki, Tomohito; Shibuya, Masatoshi; Kanoh, Naoki;  
 Iwabuchi, Yoshiharu  
 CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Tohoku  
 University, Sendai, 980-8578, Japan  
 SOURCE: Heterocycles (2010), 81(10), 2239-2246  
 CODEN: HTCYAM; ISSN: 0385-5414  
 PUBLISHER: Japan Institute of Heterocyclic Chemistry  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GRAPHIC IMAGE:



# ABSTRACT:

The enantio- and diastereocontrolled total synthesis of (-)-salinosporamide A (I), a potent 20S proteasome inhibitor, was accomplished through organocatalytic aldolization, diastereoselective Claisen condensation, a Rh-catalyzed Reformatsky reaction, and an AZADO-catalyzed oxidative  $\beta$ -lactonization reaction as the key reactions.

## IT 1258864-08-2P

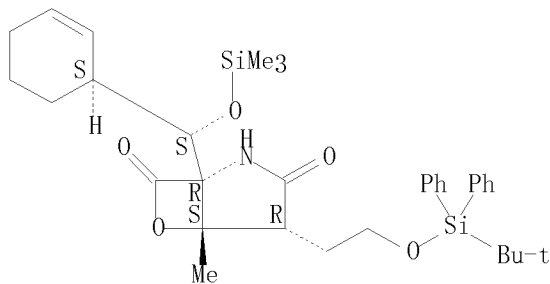
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(enantio- and diastereocontrolled synthesis of (-)-salinosporamide A via organocatalytic aldolization, diastereoselective Claisen condensation, Rh-catalyzed Reformatsky, and AZADA-catalyzed oxidative  $\beta$ -lactonization)

RN 1258864-08-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-yl[(trimethylsilyl)oxy]methyl]-4-[2-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



## IT 437742-34-2P, (-)-Salinosporamide A

RL: SPN (Synthetic preparation); PREP (Preparation)

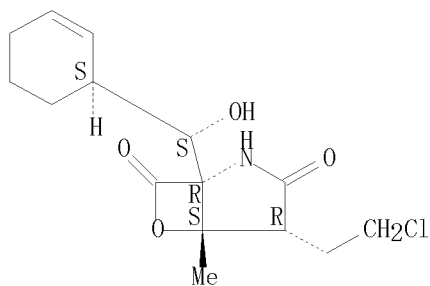
(enantio- and diastereocontrolled synthesis of (-)-salinosporamide A via organocatalytic aldolization, diastereoselective Claisen condensation, Rh-catalyzed Reformatsky, and AZADA-catalyzed oxidative  $\beta$ -lactonization)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,

(1R, 4R, 5S)- (CA INDEX NAME)

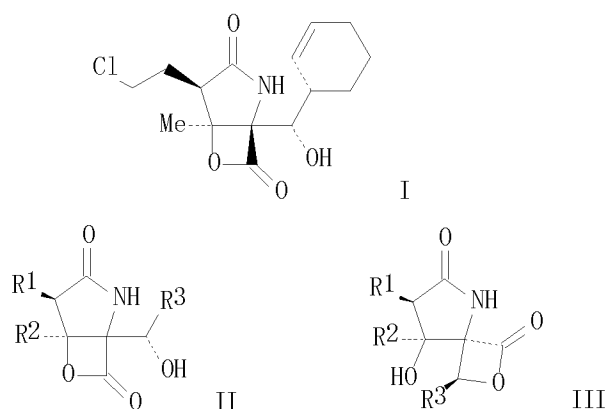
Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	1	THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT:	34	THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2010:1325926 CAPLUS  
 DOCUMENT NUMBER: 153:600599  
 TITLE: Method for asymmetric synthesis of salinosporamide A and its analog  
 INVENTOR(S): Li, Weidong; Bai, Yingjun; Chen, Li  
 PATENT ASSIGNEE(S): Nankai University, Peop. Rep. China  
 SOURCE: Faming Zhuanli Shenqing, 17pp.  
 CODEN: CNXXEV  
 DOCUMENT TYPE: Patent  
 LANGUAGE: Chinese  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 101863893	A	20101020	CN 2010-10203965	20100621
PRIORITY APPLN. INFO.:			CN 2010-10203965	20100621
OTHER SOURCE(S):	MARPAT	153:600599		
GRAPHIC IMAGE:				



# ABSTRACT:

The invention relates to a method for asym. synthesis of salinosporamide A (I) and its analogs of formula II and III. Compds. II and III, wherein R1, R2 and R3 are independent H, C1-8 (un)substituted alkyl, C2-8 (un)substituted alkenyl, C2-8 (un)substituted alkynyl, etc., are claimed. Compds. I was prepared via addition, cyclization and lactonization. The method has advantages of easily obtained materials, few steps, simple operation and large capability.

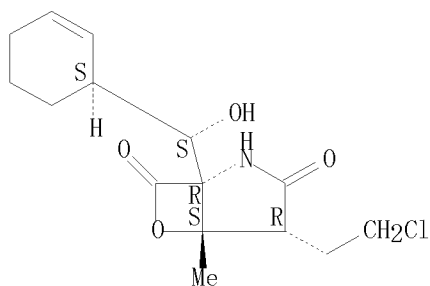
IT 437742-34-2P 823229-26-1P 1254580-09-0P  
1254580-11-4P 1254580-12-5P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (enantioselective synthesis of salinosporamide A and its analogs)

RN 437742-34-2 CAPLUS

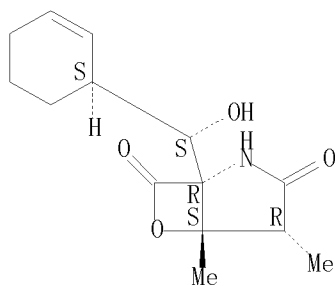
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



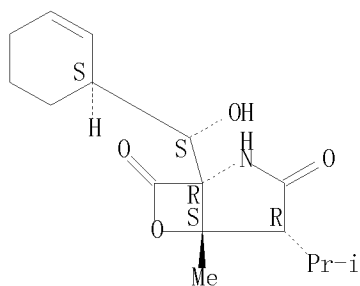
RN 823229-26-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



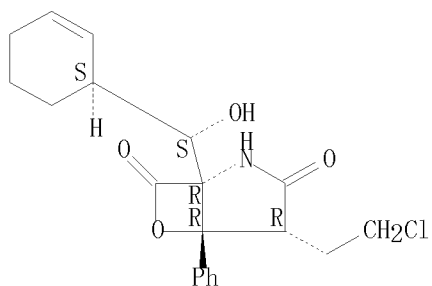
RN 1254580-09-0 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-(1-methylethyl)-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1254580-11-4 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-phenyl-,  
 (1R,4R,5R)- (CA INDEX NAME)

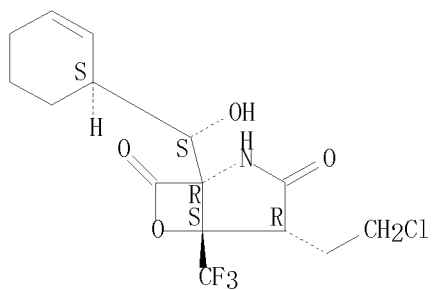
Absolute stereochemistry.



RN 1254580-12-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-(trifluoromethyl)-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

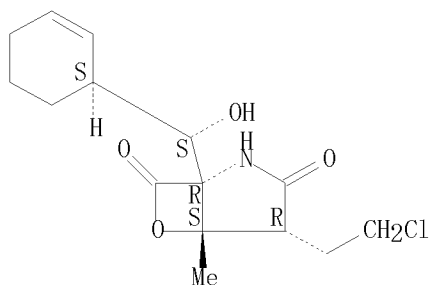


L6 ANSWER 11 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:1317440 CAPLUS  
DOCUMENT NUMBER: 154:58588  
TITLE: Characterization of 5-Chloro-5-Deoxy-D-Ribose  
1-Dehydrogenase in Chloroethylmalonyl Coenzyme A  
Biosynthesis: Substrate and reaction profiling  
AUTHOR(S): Kale, Andrew J.; McGlinchey, Ryan P.; Moore, Bradley  
S.  
CORPORATE SOURCE: Center of Marine Biotechnology and Biomedicine,  
Scripps Institution of Oceanography, University of  
California at San Diego, La Jolla, CA, 92093, USA  
SOURCE: Journal of Biological Chemistry (2010), 285(44),  
33710-33717  
CODEN: JBCHA3; ISSN: 0021-9258  
PUBLISHER: American Society for Biochemistry and Molecular  
Biology  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
ABSTRACT:

SalM is a short-chain dehydrogenase/reductase enzyme from the marine actinomycete *Salinispora tropica* that is involved in the biosynthesis of chloroethylmalonyl-CoA, a novel halogenated polyketide synthase extender unit of the proteasome inhibitor salinosporamide A. SalM was heterologously overexpressed in *Escherichia coli* and characterized in vitro for its substrate specificity, kinetics, and reaction profile. A sensitive real-time <sup>13</sup>C NMR assay was developed to visualize the oxidation of 5-chloro-5-deoxy-D-ribose to 5-chloro-5-deoxy-D-ribono-γ-lactone in an NAD<sup>+</sup>-dependent reaction, followed by spontaneous lactone hydrolysis to 5-chloro-5-deoxy-D-ribonate. Although short-chain dehydrogenase/reductase enzymes are widely regarded as metal-independent, a strong divalent metal cation dependence for Mg<sup>2+</sup>, Ca<sup>2+</sup>, or Mn<sup>2+</sup> was observed with SalM. Oxidative activity was also measured with the alternative substrates D-erythrose and D-ribose, making SalM the first reported stereospecific non-phosphorylative ribose 1-dehydrogenase.

IT **437742-34-2**, Salinosporamide A  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(biosynthesis of; characterization of 5-chloro-5-deoxy-D-ribose  
1-dehydrogenase in chloroethylmalonyl CoA biosynthesis)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2010:1316799 CAPLUS  
 DOCUMENT NUMBER: 153:571814  
 TITLE: Peptides and aptamers for targeting of neuron or nerves  
 INVENTOR(S): Tsien, Roger Y.; Nguyen, Quyen T.; Whitney, Michael  
 PATENT ASSIGNEE(S): The Regents of the University of California, USA  
 SOURCE: PCT Int. Appl., 62pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010121023	A2	20101021	WO 2010-US31231	20100415
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
PRIORITY APPLN. INFO.:			US 2009-169626P	P 20090415

## ABSTRACT:

The present invention provides methods for guiding preservation of neurons or nerves during surgery by administering a fluorescently-labeled peptide or aptamer that specifically binds to the neurons or nerves. The invention further provides targeting mols. of fluorescently-labeled peptides or aptamers that specifically bind to neurons or nerves and for compns. thereof.

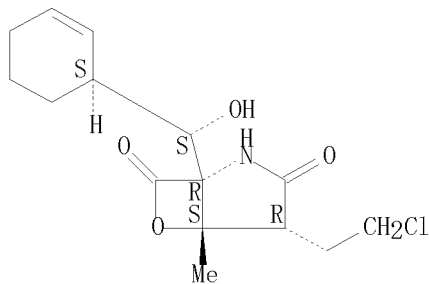
IT **437742-34-2**, Salinosporamide A

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (peptides and aptamers for targeting of neuron or nerves)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 13 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2010:1288311 CAPLUS

DOCUMENT NUMBER: 154:100662

TITLE: Novel drugs for the treatment of multiple myeloma

AUTHOR(S): Blade, Joan; Cibeira, Ma Teresa; Rosinol, Laura

CORPORATE SOURCE: Hematology and Oncology Institute, Hematology  
Department, IDIBAPS, Hospital Clinic, Barcelona, Spain

SOURCE: Haematologica (2010), 95(5), 702-704

CODEN: HAEMAX; ISSN: 0390-6078

PUBLISHER: Ferrata Storti Foundation

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ABSTRACT:

A review. The research of Atanackovic et al. (Haematologica 2010;95:785-793), entitled 'Cancer-testis antigens MAGE-C1/CT7 and MAGE-A3 promote the survival of multiple myeloma cells', is reviewed with commentary and refs. Atanackovic et al. describe the role of MAGE-C1/CT7 and MAGE-A3 in the proliferation, cell adhesion, chemosensitivity and apoptosis resulting from gene-specific silencing in myeloma cell lines. It was shown that the above-mentioned cancer testis antigens play an important role in reducing the rate of spontaneous and chemotherapy-induced apoptosis and might constitute important targets for novel anti-myeloma specific therapies. The authors hypothesize that such an approach could be particularly useful in the setting of minimal residual disease following currently available anti-myeloma therapy.

IT **437742-34-2**, NPI\_0052

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

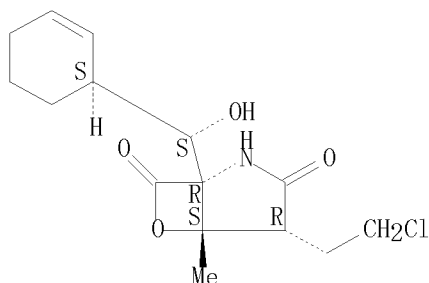
(Biological study); USES (Uses)

(NPI\_0052 may be useful in treatment of patient with multiple myeloma)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

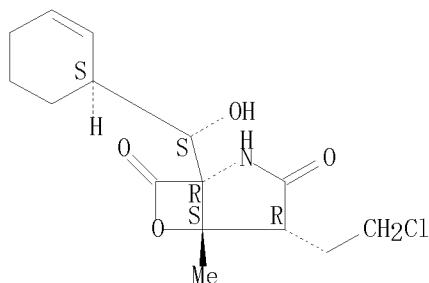


L6 ANSWER 14 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:1234865 CAPLUS  
DOCUMENT NUMBER: 153:523871  
TITLE: Prephenate Decarboxylases: A New Prephenate-Utilizing  
Enzyme Family That Performs Nonaromatizing  
Decarboxylation en Route to Diverse Secondary  
Metabolites  
AUTHOR(S): Mahlstedt, Sarah; Fielding, Elisha N.; Moore, Bradley  
S.; Walsh, Christopher T.  
CORPORATE SOURCE: Department of Biological Chemistry and Molecular  
Pharmacology, Harvard Medical School, Boston, MA,  
02115, USA  
SOURCE: Biochemistry (2010), 49(42), 9021-9023  
CODEN: BICHAW; ISSN: 0006-2960  
PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
ABSTRACT:

Prephenate is the direct precursor of phenylpyruvate and 4-hydroxyphenylpyruvate in the biogenesis of phenylalanine and tyrosine by action of the decarboxylative, aromatizing enzymes prephenate dehydratase and dehydrogenase, resp. The recent characterization of BacA in bacilysin biosynthesis as a nonaromatizing decarboxylase reveals a new route from prephenate in the biosynthesis of nonproteinogenic amino acids. This study describes two addnl. enzymes, AerD from *Planktothrix agardhii* and SalX from *Salinispora tropica*, that utilize the central building block prephenate for flux down distinct pathways to amino acid products, representing a new metabolic fate for prephenate and establishing a new family of nonaromatizing prephenate decarboxylases.

IT **437742-34-2**, Salinosporamide A  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(prephenate decarboxylases: A new prephenate-utilizing enzyme family  
that performs nonaromatizing decarboxylation en route to diverse  
secondary metabolites)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2010:1148832 CAPLUS

TITLE: Proteasome inhibitors prevent caspase-1-mediated disease in rodents challenged with anthrax lethal toxin

AUTHOR(S): Muehlbauer, Stefan M.; Lima, Heriberto, Jr.; Goldman, David L.; Jacobson, Lee S.; Rivera, Johanna; Goldberg, Michael F.; Palladino, Michael A.; Casadevall, Arturo; Brojatsch, Juergen

CORPORATE SOURCE: Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY, USA

SOURCE: American Journal of Pathology (2010), 177(2), 735-743  
CODEN: AJPA44; ISSN: 0002-9440

PUBLISHER: American Society for Investigative Pathology

DOCUMENT TYPE: Journal

LANGUAGE: English

## ABSTRACT:

NOD-like receptors (NLRs) and caspase-1 are critical components of innate immunity, yet their over-activation has been linked to a long list of microbial and inflammatory diseases, including anthrax. The *Bacillus anthracis* lethal toxin (LT) has been shown to activate the NLR Nalpb and caspase-1 and to induce many symptoms of the anthrax disease in susceptible murine strains. In this study we tested whether it is possible to prevent LT-mediated disease by pharmacol. inhibition of caspase-1. We found that caspase-1 and proteasome inhibitors blocked LT-mediated caspase-1 activation and cytolysis of LT-sensitive (Fischer and Brown-Norway) rat macrophages. The proteasome inhibitor NPI-0052 also prevented disease progression and death in susceptible Fischer rats and increased survival in BALB/c mice after LT challenge. In addition, NPI-0052 blocked rapid disease progression and death in susceptible Fischer rats and BALB/c mice challenged with LT. In contrast, Lewis rats, which harbor LT-resistant macrophages, showed no signs of caspase-1 activation after LT injection and did not exhibit rapid disease progression. Taken together, our findings indicate that caspase-1 activation is critical for rapid disease progression in rodents challenged with LT. Our studies indicate that pharmacol. inhibition of NLR signaling and caspase-1 can be used to treat inflammatory diseases.

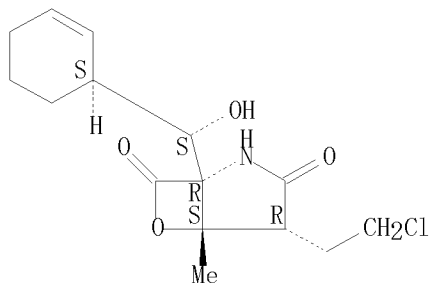
IT INDEXING IN PROGRESS

IT 437742-34-2, NPI-0052RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(proteasome inhibitors prevent caspase-1-mediated disease in rodents challenged with anthrax lethal toxin)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT:

46

THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2010:1096413 CAPLUS  
 DOCUMENT NUMBER: 153:351079  
 TITLE: Non-covalent inhibition of the 26s proteasome and uses thereof  
 INVENTOR(S): Tepe, Jetze; Lansdell, Theresa; Karin, Michael  
 PATENT ASSIGNEE(S): Michigan State University, USA  
 SOURCE: PCT Int. Appl., 60pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010099445	A2	20100902	WO 2010-US25590	20100226
WO 2010099445	A3	20110127		
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
PRIORITY APPLN. INFO.:			US 2009-155884P	P 20090226

## ABSTRACT:

The present inventions relate to compns. and methods for treating inflammatory diseases and cancer by administering proteasome inhibitors. In particular, the present inventions provide a new class of orally available non-covalent proteasome inhibitors capable of reducing NF- $\kappa$ B for mediating cytokine production in vivo. Further, the use of a small mol. weight inhibitor of the 26S proteasome via a non-covalent type inhibition is contemplated for use as a means to treat NF- $\kappa$ B mediated diseases, including but not limited to multiple myeloma and rheumatoid arthritis.

IT 437742-34-2, NPI-0052

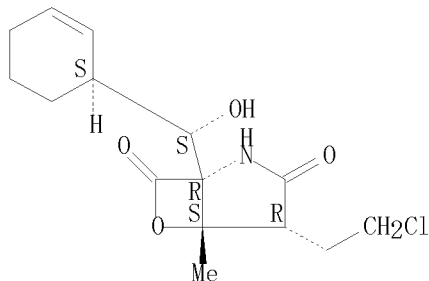
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(non-covalent inhibition of 26s proteasome by imidazolines and uses to treat NF- $\kappa$ B-mediated diseases such as inflammatory diseases and cancer)

RN 437742-34-2 CAPLUS

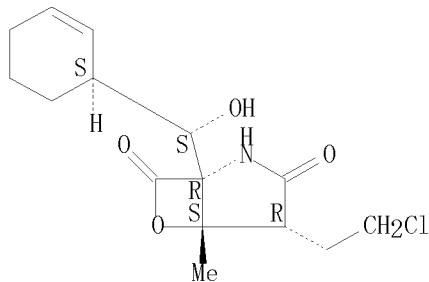
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 17 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:873504 CAPLUS  
DOCUMENT NUMBER: 153:194722  
TITLE: Caspase 8: Mediating the effects of a novel proteasome inhibitor, NPI-0052  
AUTHOR(S): Miller, Claudia Patricia  
CORPORATE SOURCE: Health Science Center, Univ. of Texas, Houston, TX, USA  
SOURCE: (2009) 148 pp. Avail.: UMI, Order No. DA3367968  
From: Diss. Abstr. Int., B 2010, 70(7), 3942  
DOCUMENT TYPE: Dissertation  
LANGUAGE: English  
ABSTRACT: Unavailable  
IT **437742-34-2**, NPI-0052  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(caspase 8, mediating the effects of a novel proteasome inhibitor, NPI-0052)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 18 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:860631 CAPLUS  
TITLE: Progress of prevention and treatment of insulin  
resistance after surgery  
AUTHOR(S): Zhu, Xuan-Jin; Liu, Jian-wei  
CORPORATE SOURCE: Department of General Surgery, Affiliated Guangzhou  
Red Cross Hospital, Jinan University, Guangzhou,  
510220, Peop. Rep. China  
SOURCE: Zhonghua Putong Waikexue Wenxian, Dianshiban (2010),  
4(2), 49-51  
CODEN: ZPWWAE; ISSN: 1674-0793  
PUBLISHER: Zhonghua Yixue Dianzi Yinxian Chubanshe  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: Chinese  
ABSTRACT:

A review with 20 refs. The topics discussed include: (1) the adjuvant chemotherapy, radiotherapy and chemotherapy of pancreatic neoplasm after surgery; (2) the novel adjuvant radiotherapy and chemotherapy of pancreatic neoplasm before surgery; (3) the radiotherapy and chemotherapy for local advanced pancreatic neoplasm; (4) the palliative chemotherapy of advanced pancreatic neoplasm; and (5) the mol. targeted treatment of pancreatic neoplasm.

IT INDEXING IN PROGRESS

IT **437742-34-2**, Salinosporamide A

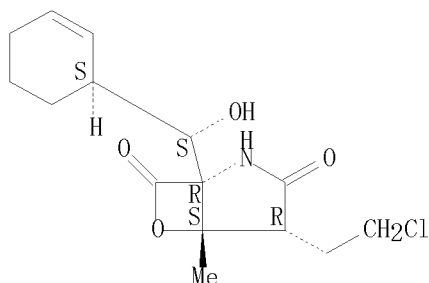
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(research progress on the radiotherapy and chemotherapy of pancreatic neoplasm and its treatment with mol. targeted drug)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 19 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2010:788322 CAPLUS  
TITLE: Peripheral neuropathy during bortezomib treatment of multiple myeloma: a review of recent studies  
AUTHOR(S): Cavaletti, Guido; Jakubowiak, Andrzej J.  
CORPORATE SOURCE: University of Milan-Bicocca, Monza, Italy  
SOURCE: Leukemia & Lymphoma (2010), 51(7), 1178-1187  
CODEN: LELYEA; ISSN: 1042-8194  
PUBLISHER: Informa Healthcare  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

Treatment-emergent peripheral neuropathy (PN) is an important dose-limiting toxicity during treatment of multiple myeloma (MM). Bortezomib-induced PN (BIPN) occurred in 37-44% of clin. trial patients with MM, with the cumulative treatment dose as its single most significant predictor. This review discusses the clin. profile of BIPN in the treatment of MM and guidelines for its management. Lower rates of BIPN observed during treatment of solid tumors compared with rates of hematol. cancers are also discussed. Several areas of research are reviewed that may improve the management of BIPN, including co-therapies with the novel heat shock protein inhibitor tanespimycin, which appears to reduce the incidence of BIPN, and recent studies with second-generation proteasome inhibitors such as carfilzomib and NPI-0052. Adherence to the National Cancer Institute dose-modification algorithm is the most effective method for mitigating BIPN. Reversal of BIPN after treatment cessation occurs in most cases, but recovery in some patients takes as long as 1.7 years, and some individuals fail to return to baseline neurol. function. BIPN can cause a significant reduction in quality of life, primarily due to severe treatment-emergent pain. Ongoing research may provide addnl. information about the mechanism of BIPN and strategies to reduce PN.

IT INDEXING IN PROGRESS

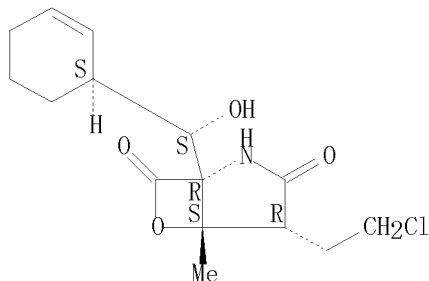
IT 437742-34-2, NPI-0052

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(peripheral neuropathy during bortezomib treatment of multiple myeloma)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 20 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:782974 CAPLUS  
DOCUMENT NUMBER: 153:137435  
TITLE: Distinct Biological Network Properties between the  
Targets of Natural Products and Disease Genes  
AUTHOR(S): Dancik, Vlado; Seiler, Kathleen Petri; Young, Damian  
W.; Schreiber, Stuart L.; Clemons, Paul A.  
CORPORATE SOURCE: Broad Institute of Harvard and MIT, Cambridge, MA,  
02143, USA  
SOURCE: Journal of the American Chemical Society (2010),  
132(27), 9259-9261  
CODEN: JACSAT; ISSN: 0002-7863  
PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
ABSTRACT:

We show that natural products target proteins with a high number of protein-protein functional interactions (high biol. network connectivity) and that these protein targets have higher network connectivity than disease genes. This feature may facilitate disruption of essential biol. pathways, resulting in competitor death. This result also suggests that addnl. sources of small mols. will be required to discover drugs targeting the root causes of human disease in the future.

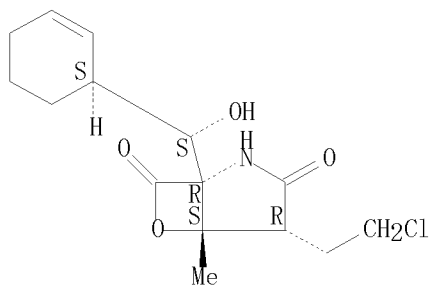
IT **437742-34-2**, Salinosporamide A

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(as natural product; natural products target proteins with high number of protein-protein functional interactions (high biol. network connectivity) and these protein targets have higher network connectivity than disease genes)

RN 437742-34-2 CAPLUS

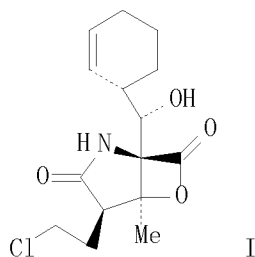
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD  
(4 CITINGS)  
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 21 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2010:770464 CAPLUS  
 DOCUMENT NUMBER: 153:310990  
 TITLE: A1,3-strain enabled retention of chirality during  
 bis-cyclization of  $\beta$ -ketoamides: total synthesis  
 of (-)-salinosporamide A and (-)-homosalinosporamide A  
 AUTHOR(S): Nguyen, Henry; Ma, Gil; Romo, Daniel  
 CORPORATE SOURCE: Department of Chemistry, Texas A&M University, College  
 Station, TX, 77840, USA  
 SOURCE: Chemical Communications (Cambridge, United Kingdom)  
 (2010), 46(26), 4803-4805  
 CODEN: CHCOFS; ISSN: 1359-7345  
 PUBLISHER: Royal Society of Chemistry  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GRAPHIC IMAGE:

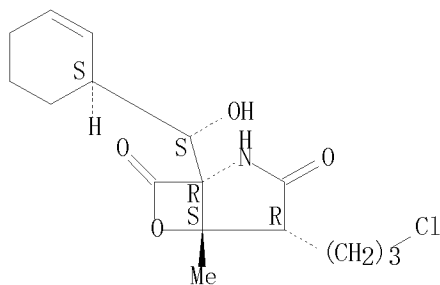


## ABSTRACT:

A concise, enantioselective synthesis of the Phase I anticancer agent, (-)-salinosporamide A (I), is described. The brevity of the described strategy stems from a key bis-cyclization of a  $\beta$ -keto tertiary amide, accomplished on gram scale, which retains optical purity enabled by A1,3-strain rendering epimerization slow relative to the rate of bis-cyclization. The versatility of the strategy for derivative synthesis is demonstrated by the synthesis of (-)-homosalinosporamide A.

IT 1239987-24-6P, (-)-Homosalinosporamide A  
 RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)  
 (crystal structure; enantioselective total synthesis of  
 (-)-salinosporamide A and (-)-homosalinosporamide A via  
 bis-cyclization)  
 RN 1239987-24-6 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(3-chloropropyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

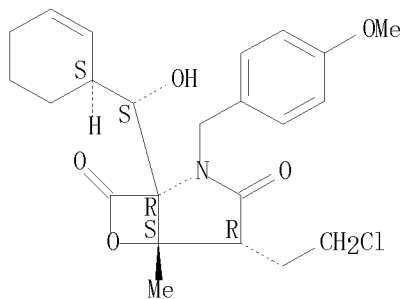


IT 1239897-10-9P 1239897-16-5P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (enantioselective total synthesis of (-)-salinosporamide A and  
 (-)-homosalinosporamide A via bis-cyclization)  
 RN 1239897-10-9 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,



4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-2-[(4-methoxyphenyl)methyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

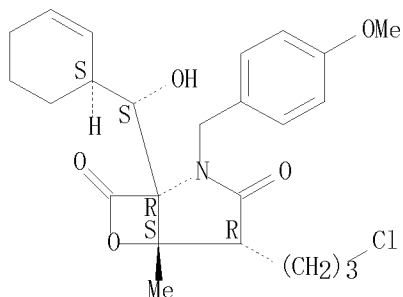
Absolute stereochemistry.



RN 1239897-16-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(3-chloropropyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-2-[(4-methoxyphenyl)methyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



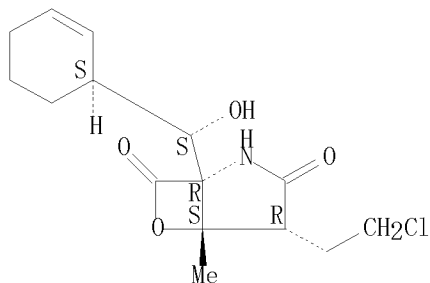
IT **437742-34-2P**, (-)-Salinosporamide A

RL: SPN (Synthetic preparation); PREP (Preparation)  
(enantioselective total synthesis of (-)-salinosporamide A and  
(-)-homosalinosporamide A via bis-cyclization)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	7	THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT:	35	THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 22 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2010:763956 CAPLUS

DOCUMENT NUMBER: 154:101031

TITLE: Pharmacodynamic and efficacy studies of the novel proteasome inhibitor NPI-0052 (marizomib) in a human plasmacytoma xenograft murine model

AUTHOR(S): Singh, Ajita V.; Palladino, Michael A.; Lloyd, George Kenneth; Potts, Barbara C.; Chauhan, Dharminder; Anderson, Kenneth C.

CORPORATE SOURCE: The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Myeloma Center, Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

SOURCE: British Journal of Haematology (2010), 149(4), 550-559  
CODEN: BJHEAL; ISSN: 0007-1048

PUBLISHER: Wiley-Blackwell

DOCUMENT TYPE: Journal

LANGUAGE: English

# ABSTRACT:

Our previous study showed that the novel proteasome inhibitor NPI-0052 induces apoptosis in multiple myeloma (MM) cells resistant to conventional and bortezomib (Velcade, Takeda, Boston, MA, USA) therapies. In vivo studies using human MM-xenografts demonstrated that NPI-0052 is well tolerated, prolongs survival, and reduces tumor recurrence. These preclin. studies provided the basis for an ongoing phase-1 clin. trial of NPI-0052 in relapsed/refractory MM patients. Here we performed pharmacodynamic (PD) studies of NPI-0052 using human MM xenograft murine model. Our results showed that NPI-0052: (i) rapidly left the vascular compartment in an active form after i.v. administration, (ii) inhibited 20S proteasome chymotrypsin-like (CT-L,  $\beta 5$ ), trypsin-like (T-L,  $\beta 2$ ), and caspase-like (C-L,  $\beta 1$ ) activities in extra-vascular tumors, packed whole blood (PWB), lung, liver, spleen, and kidney, but not brain and (iii) triggered a more sustained (>24 h). Tissue distribution anal. of radiolabeled compound (3H-NPI-0052) in mice demonstrated that NPI-0052 left the vascular space and entered organs as the parent compound. Importantly, treatment of MM.1S-bearing mice with NPI-0052 showed reduced tumor growth without significant toxicity, which was associated with prolonged inhibition of proteasome activity in tumors and PWB but not normal tissues.

IT 437742-34-2, NPI-0052

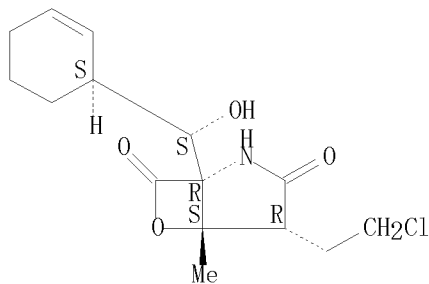
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmacodynamic and efficacy studies of novel proteasome inhibitor NPI-0052 in human plasmacytoma xenograft murine model)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

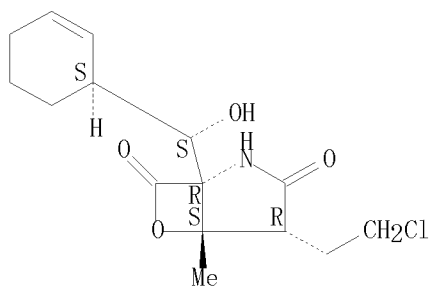
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 23 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:737549 CAPLUS  
DOCUMENT NUMBER: 153:471367  
TITLE: Proteasome inhibition as a therapeutic strategy in  
patients with multiple myeloma  
AUTHOR(S): Fuchs, Ota  
CORPORATE SOURCE: Institute of Hematology and Blood Transfusion, Prague  
2, 128 20, Czech Rep.  
SOURCE: Multiple Myeloma (2009), 101-125. Editor(s):  
Georgiev, Milen; Bachev, Evgeni. Nova Science  
Publishers, Inc.: Hauppauge, N. Y.  
CODEN: 69MVM2; ISBN: 978-1-60876-108-1  
DOCUMENT TYPE: Conference; General Review  
LANGUAGE: English  
ABSTRACT:

A review. Multiple myeloma (MM) is the second most frequent hematol. malignancy and remains fatal despite all available therapies, because of chemotherapeutic resistance. Novel targeted drugs for the treatment of MM are therefore needed to improve outcome of MM patients. Bortezomib (PS-341, Velcade; Millennium Pharmaceuticals, Cambridge MA), a dipeptidyl boronic acid that reversibly inhibits the chymotrypsin-like activity in the 20S core of the 26S mammalian proteasome, is the first proteasome inhibitor that was approved by the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA) for patients with relapsed and refractory MM who had received at least one prior therapy and who had already undergone or are unsuitable for the transplantation of bone marrow. Phase I-III trials based on previous preclin. studies showed very good antimyeloma activity. Bortezomib acts by disrupting various cell signaling pathways, thereby leading to cell cycle arrest, apoptosis, and inhibition of angiogenesis. The main action of bortezomib is the inhibition of the key transcription factor, nuclear factor-kappaB (NF- $\kappa$ B) activation. Activation of NF- $\kappa$ B has been noted in MM cells. Bortezomib interferes with NF- $\kappa$ B-mediated cell survival, tumor growth and angiogenesis. Several studies have shown that cancer cells are more sensitive than normal cells to the proapoptotic effects of bortezomib, perhaps due to their loss of checkpoint mechanisms for DNA repair. The accumulation of misfolded proteins in the endoplasmic reticulum (ER) leads to the induction of the unfolded protein response, provoking apoptosis. Proteasome inhibitors induce ER-mediated apoptosis. The increased susceptibility of MM cells to ER stress is caused by the large amts. of Igs produced by MM cells. The clin. success of bortezomib is encouraging. Bortezomib is relatively well tolerated, causing manageable nonhematol. and hematol. toxicity. However, the overall response rate was 40-50% and bortezomib resistance was also observed. Response rates may be improved with combination therapy (bortezomib with dexamethasone, thalidomide, lenalidomide, arsenic trioxide, cisplatin, doxorubicin, cyclophosphamide, etoposide or with melphalan and prednisone). Clin. evaluation of addnl. proteasome inhibitors of the next generation with greater efficacy is also needed. Three such proteasome inhibitors (carfilzomib, salinosporamide A and threonine boronic acid-derived proteasome inhibitor CEP-18770) have been recently tested in preclin. models of MM. Carfilzomib (PR-171; Proteolix), an epoxyketone related to epoxomicin inhibits the chymotrypsin-like proteasome activity as bortezomib does. However, carfilzomib is an irreversible inhibitor of all three proteasome proteolytic sites. Salinosporamide A (NPI-0052), a compound related to lactacystin binds irreversibly to the 20S proteasome and acts predominantly through caspase-8 activation. CEP-18770 is a reversible inhibitor of the chymotrypsin-like proteasome activity as bortezomib but it inhibits also the tryptic and peptidyl glutamyl activities of the proteasome.

IT **437742-34-2**, Salinosporamide A  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(proteasome inhibition as a therapeutic strategy in patients with  
multiple myeloma)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

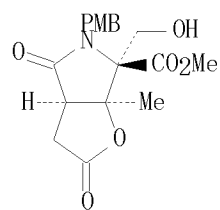
Absolute stereochemistry. Rotation (-).



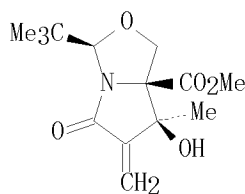
REFERENCE COUNT:

104 THERE ARE 104 CITED REFERENCES AVAILABLE FOR  
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

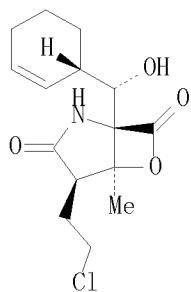
L6 ANSWER 24 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2010:597019 CAPLUS  
 DOCUMENT NUMBER: 153:62054  
 TITLE: Concise Formal Synthesis of (-)-Salinosporamide A  
 (Marizomib) Using a Regio- and Stereoselective  
 Epoxidation and Reductive Oxirane Ring-Opening  
 Strategy  
 AUTHOR(S): Ling, Taotao; Potts, Barbara C.; Macherla, Venkat R.  
 CORPORATE SOURCE: Nereus Pharmaceuticals, Inc., San Diego, CA, 92121,  
 USA  
 SOURCE: Journal of Organic Chemistry (2010), 75(11), 3882-3885  
 CODEN: JOCEAH; ISSN: 0022-3263  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 153:62054  
 GRAPHIC IMAGE:



I



II



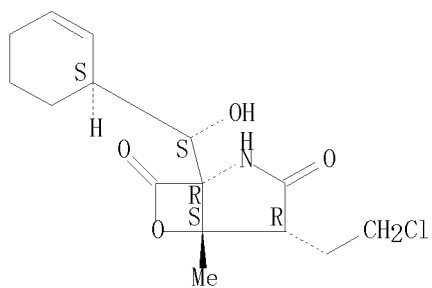
III

## ABSTRACT:

Dioxofuranopyrrolidonecarboxylate I (PMB = 4-MeOC6H4CH2) and spirooxiranepyrrolidonecarboxylate II are prepared, completing formal total syntheses of the 20S proteasome inhibitor (-)-salinosporamide A (marizomib; NPI-0052; III) using stereoselective epoxidn. and reductive ring-opening reactions as key steps. The structure of the enantiomer of a furanopyrrolidonecarboxylate intermediate in the formal synthesis of III is determined by X-ray crystallog. Appropriate safety equipment and precautions should be used when concentrating 5-6 M tert-Bu hydroperoxide for the key epoxidn. reaction in the preparation of I.

IT 437742-34-2P, (-)-Salinosporamide A  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (formal total synthesis of salinosporamide A (marizomib) using  
 stereoselective epoxidn. and reductive epoxide ring opening reactions  
 as key steps)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD  
(7 CITINGS)  
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 25 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2010:566345 CAPLUS  
 DOCUMENT NUMBER: 152:545922  
 TITLE: Methods of fibrosis diagnosing by measuring H3K27  
 trimethylation and EZH2 or YY-1 expression and  
 fibrosis treating by inhibition of the same  
 INVENTOR(S): Guo, Jia; Lin, Xin; Georas, Steve; Sime, Patricia  
 PATENT ASSIGNEE(S): University of Rochester, USA  
 SOURCE: PCT Int. Appl., 107pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010051550	A1	20100506	WO 2009-US63016	20091102
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
PRIORITY APPLN. INFO. :			US 2008-110267P	P 20081031

## ABSTRACT:

The present invention is directed to methods of diagnosing and treating a fibrotic condition, particularly pulmonary fibrosis, in a mammalian subject. These methods involve measuring the levels of trimethylation at lysine residue 27 of histone H3 (H3K27) and/or measuring the expression levels of enhancer of zeste homolog 2 (EZH2) or Yin-Yang-1 (YY-1, GATA-1). Agents inhibiting histone methylation or EZH2 or YY-1 expression useful for treating fibrosis or a fibrotic condition are also disclosed.

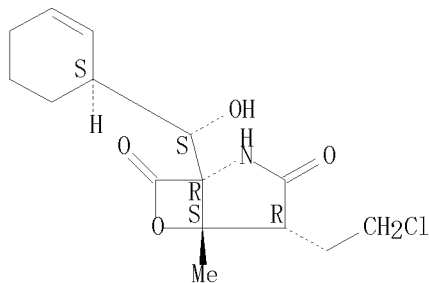
IT 437742-34-2

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (as YY-1 inhibitor; methods of fibrosis diagnosing by measuring H3K27  
 trimethylation and EZH2 or YY-1 expression and fibrosis treating by  
 inhibition of same)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 26 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:565531 CAPLUS  
DOCUMENT NUMBER: 152:546548  
TITLE: Use of anti-CS1 (SLAMF7) antibodies for treatment of  
rare lymphomas  
INVENTOR(S): AFar, Daniel; Hsi, Eric  
PATENT ASSIGNEE(S): Facet Biotech Corporation, USA; Cleveland Clinic  
SOURCE: PCT Int. Appl., 63pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010051391	A1	20100506	WO 2009-US62648	20091029
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
PRIORITY APPLN. INFO.:			US 2008-110295P US 2008-118244P	P 20081031 P 20081126

## ABSTRACT:

The invention provides antibodies to tumor-associated protein CS1 (CD2-subset 1, SLAMF7, CRACC) that is shown here to express in rare lymphomas, such as natural killer (NK) cell lymphomas, nasal type NK/T-cell lymphomas, and angioimmunoblastic T-cell lymphomas (AITL). The invention provides a method of using anti-CS1 antibodies (Luc63, HuLuc63 (Elotuzumab), Luc90, Luc34, LucX.2), alone or in combination with other agents, for the treatment of rare lymphomas.

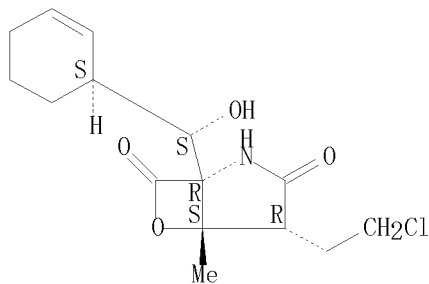
IT **437742-34-2**, NPI0052

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(co-therapy with; use of anti-CS1 (SLAMF7) antibodies for treatment of rare lymphomas)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 27 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2010:530768 CAPLUS  
 DOCUMENT NUMBER: 152:517956  
 TITLE: Methods using romidepsin and steroidal agents of treatment of lymphomas associated with expression of Bcl-2 and Bcl-XL  
 INVENTOR(S): Keegan, Mitchell; Johnstone, Ricky W.; Newbold, Andrea; Cluse, Leonie  
 PATENT ASSIGNEE(S): Gloucester Pharmaceuticals, USA; Peter MacCallum Cancer Centre  
 SOURCE: PCT Int. Appl., 71pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010047714	A1	20100429	WO 2008-US81107	20081024
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRIORITY APPLN. INFO.: WO 2008-US81107 20081024

#### ABSTRACT:

The invention provides therapy for treating cancers, such as Bcl-2+ cancers, and Bcl-XL - cancers, and other neoplasms, using romidepsin and steroidal agents. The invention provides, inter alia, methods of treating lymphomas, e.g., lymphomas characterized by one or more of Bcl-2 expression, lack of overexpression of Bcl-XL, lack of overexpression of P-glycoprotein, with romidepsin. In some embodiments, the lymphoma is a cutaneous T cell lymphoma. In some embodiments, the lymphoma is a peripheral T cell lymphoma. Romidepsin can be administered a dosages ranging from 0.5 mg/m<sup>2</sup> to approx. 28 mg/m<sup>2</sup> (e.g., from 1 mg/m<sup>2</sup> to 15 mg/m<sup>2</sup>, from 4 mg/m<sup>2</sup> to 15 mg/m<sup>2</sup>, from 8 mg/m<sup>2</sup> to 14 mg/m<sup>2</sup>, or from 4 mg/m<sup>2</sup> to approx. 10 mg/m<sup>2</sup>). Romidepsin can be administered with a second agent, such as a cytotoxic agent, a steroidal agent, a proteasome inhibitor, or a kinase inhibitor.

IT **437742-34-2**, Salinosporamide A

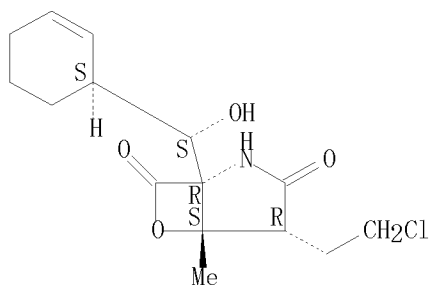
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(NPI-0052; methods using romidepsin and steroidal agents of treatment of lymphomas associated with expression of Bcl-2 and Bcl-XL)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT:

6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 28 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2010:453168 CAPLUS

DOCUMENT NUMBER: 153:276628

TITLE: Generating a generation of proteasome inhibitors: From microbial fermentation to total synthesis of salinosporamide A (marizomib) and other salinosporamides

AUTHOR(S): Potts, Barbara C.; Lam, Kin S.

CORPORATE SOURCE: Nereus Pharmaceuticals, Inc., San Diego, CA, 92121, USA

SOURCE: Marine Drugs (2010), 8, 835-880

CODEN: MDARE6; ISSN: 1660-3397

URL: <http://www.mdpi.com/1660-3397/8/4/835/pdf>

PUBLISHER: MDPI Center

DOCUMENT TYPE: Journal; General Review; (online computer file)

LANGUAGE: English

ABSTRACT:

A review. The salinosporamides are potent proteasome inhibitors among which the parent marine-derived natural product salinosporamide A (marizomib; NPI-0052; 1) is currently in clin. trials for the treatment of various cancers. Methods to generate this class of compds. include fermentation and natural products chemical, precursor-directed biosynthesis, mutasynthesis, semi-synthesis, and total synthesis. The end products range from biochem. tools for probing mechanism of action to clin. trials materials; in turn, the considerable efforts to produce the target mols. have expanded the technologies used to generate them. Here, the full complement of methods is reviewed, reflecting remarkable contributions from scientists of various disciplines over a period of 7 years since the first publication of the structure of 1.

IT 437742-34-2, Salinosporamide A

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

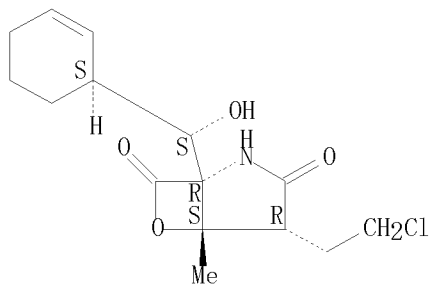
(total synthesis of salinosporamide A (marizomib), a proteasome inhibitor and other salinosporamides from microbial fermentation)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,

4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 29 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:391739 CAPLUS  
DOCUMENT NUMBER: 153:52686  
TITLE: Classification and synthesis of ubiquitin-proteasome inhibitor  
AUTHOR(S): Li, Jing; Zhang, Dayong; Wu, Xiaoming  
CORPORATE SOURCE: School of Pharmacy, China Pharmaceutical University, Nanjing, 210009, Peop. Rep. China  
SOURCE: Yaoxue Xuebao (2009), 44(12), 1313-1319  
CODEN: YHHPAL; ISSN: 0513-4870  
PUBLISHER: Yaoxue Xuebao Bianjibu  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: Chinese  
ABSTRACT:

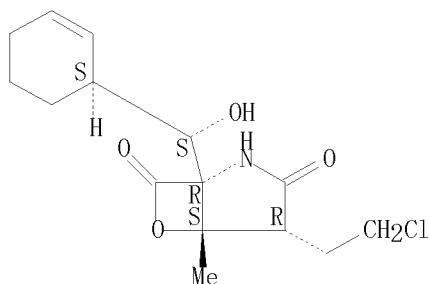
This review with 30 refs. is given on the main results from the use of proteasome inhibition in cancer chemotherapy, the structure of several proteasome inhibitors and their synthesis. The inhibition of protein degradation through the ubiquitin-proteasome pathway is a recently developed approach to cancer treatment, which extends the range of cellular target for chemotherapy. This therapeutic strategy is very interesting since the proteasomes carry out the regulated degradation of unnecessary or damaged cellular proteins, a process that is dysregulated in many cancer cells. Based on this hypothesis, the proteasome complex inhibitor Bortezomib was approved for use in multiple myeloma patients by FDA in 2003. Drug discovery programs in academy and the pharmaceutical industry have developed a range of synthetic and natural inhibitors of the 20S proteasome core particle that have entered human clin. trials as significant anti-cancer leads.

IT **437742-34-2**, Salinosporamide A  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(classification and synthesis of ubiquitin-proteasome inhibitor)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 30 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:318415 CAPLUS  
DOCUMENT NUMBER: 153:324292  
TITLE: Building on bortezomib: second-generation proteasome inhibitors as anti-cancer therapy  
AUTHOR(S): Dick, Lawrence R.; Fleming, Paul E.  
CORPORATE SOURCE: Millennium Pharmaceuticals, Inc., Cambridge, MA, 02139, USA  
SOURCE: Drug Discovery Today (2010), 15(5/6), 243-249  
CODEN: DDTQFS; ISSN: 1359-6446  
PUBLISHER: Elsevier B.V.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

A review. Inhibition of the proteasome (a highly abundant enzymic complex responsible for intracellular protein turnover) is an effective anti-cancer therapeutic approach, as demonstrated by the first-in-class agent bortezomib. Various new proteasome inhibitors are now in development, including peptide boronic acid analogs MLN9708 and CEP-18770, peptide epoxyketones carfilzomib and PR-047, and NPI-0052, a  $\beta$ -lactone compound. All are potent inhibitors of proteasome activity in vitro but show differences in enzyme binding kinetics, which might affect their pharmacol. and result in different efficacy and safety profiles. Here, we review the second-generation proteasome inhibitors and assess the potential pharmacol. impact of their different chemical properties.

IT **437742-34-2**, NPI-0052

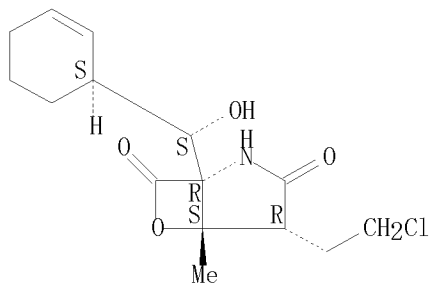
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(bortezomib and  $\beta$ -lactone NPI-0052 served as potent inhibitors of proteasome activity with different enzyme binding kinetics resulting in difference in efficacy and safety profiles)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

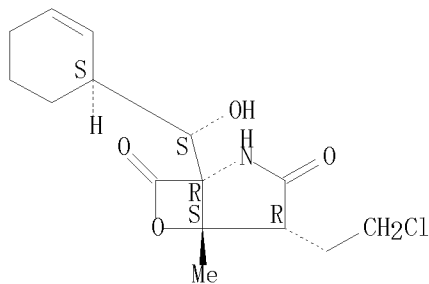
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 31 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:286014 CAPLUS  
DOCUMENT NUMBER: 152:541281  
TITLE: Activation of EGFR by proteasome inhibition requires  
HB-EGF in pancreatic cancer cells  
AUTHOR(S): Sloss, C. M.; Wang, F.; Palladino, M. A.; Cusack, J.  
C., Jr.  
CORPORATE SOURCE: Department of Surgery, Division of Surgical Oncology,  
Massachusetts General Hospital, Harvard Medical  
School, Boston, MA, USA  
SOURCE: Oncogene (2010), 29(21), 3146-3152  
CODEN: ONCNES; ISSN: 0950-9232  
PUBLISHER: Nature Publishing Group  
DOCUMENT TYPE: Journal  
LANGUAGE: English

ABSTRACT:  
Resistance to drug treatments underlies the high lethality of pancreatic ductal adenocarcinoma. Along with others, we have recently identified that proteasome inhibition is a promising therapeutic option in this highly refractory disease. The pleiotropic effects of proteasome inhibition include the activation of apoptotic signaling pathways and also antiapoptotic signaling pathways such as EGFR, AKT and the MAP kinases that reduce the apoptotic potential of this class of drug. In this study, we sought to determine the mechanism behind the activation of EGFR in response to proteasome inhibition in pancreatic cancer cells. We found that the second-generation proteasome inhibitor NPI-0052 induced the mRNA transcription of several EGFR family ligands (EGF, HB-EGF and epiregulin), however only increases in HB-EGF were detected at the protein level. Using both pharmacol. inhibitors and lentiviral-mediated shRNA knockdown of EGFR ligand expression, we discovered that ligand cleavage by MMP/ADAMs and HB-EGF expression is required for activation of EGFR in response to proteasome inhibition. Furthermore, we discover that induction of HB-EGF is dependent on reactive oxygen species and p38-MAPK signaling but not ERK and that the transcription factor SP-1 is involved in NPI-0052-induced HB-EGF transcription. Together, these results indicate that stress signaling leading to induction of HB-EGF expression and increases in MMP/ADAM-dependent HB-EGF cleavage are responsible for proteasome inhibitor-induced activation of EGFR in pancreatic cancer cells.

IT 437742-34-2, NPI-0052  
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(activation of EGFR by proteasome inhibition requires HB-EGF in pancreatic cancer cells)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 32 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2010:165189 CAPLUS

DOCUMENT NUMBER: 153:325064

TITLE: Combination of novel proteasome inhibitor NPI-0052 and lenalidomide trigger in vitro and in vivo synergistic cytotoxicity in multiple myeloma

AUTHOR(S): Chauhan, Dharminder; Singh, Ajita V.; Ciccarelli, Bryan; Richardson, Paul G.; Palladino, Michael A.; Anderson, Kenneth C.

CORPORATE SOURCE: LeBow Institute for Myeloma Therapeutics and Jerome Lipper Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

SOURCE: Blood (2010), 115(4), 834-845  
CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: American Society of Hematology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Our recent study demonstrated that a novel proteasome inhibitor NPI-0052 is distinct from bortezomib (Velcade) and, importantly, triggers apoptosis in multiple myeloma (MM) cells resistant to bortezomib. Here we demonstrate that combining NPI-0052 and lenalidomide (Revlimid) induces synergistic anti-MM activity in vitro using MM-cell lines or patient MM cells. NPI-0052 plus lenalidomide-induced apoptosis is associated with (1) activation of caspase-8, caspase-9, caspase-12, caspase-3, and poly(ADP) ribose polymerase; (2) activation of BH-3 protein BIM; (3) translocation of BIM to endoplasmic reticulum; (4) inhibition of migration of MM cells and angiogenesis; and (5) suppression of chymotrypsin-like, caspase-like, and trypsin-like proteasome activities. Importantly, blockade of BIM using siRNA significantly abrogates NPI-0052 plus lenalidomide-induced apoptosis. Furthermore, studies using biochem. inhibitors of caspase-8 vs. caspase-9 demonstrate that NPI-0052 plus lenalidomide-triggered apoptosis is primarily dependent on caspase-8 signaling. In animal tumor model studies, low-dose combination of NPI-0052 and lenalidomide is well tolerated, significantly inhibits tumor growth, and prolongs survival. Taken together, our study provides the preclin. rationale for clin. protocols evaluating lenalidomide together with NPI-0052 to improve patient outcome in MM.

IT **437742-34-2**, NPI-0052

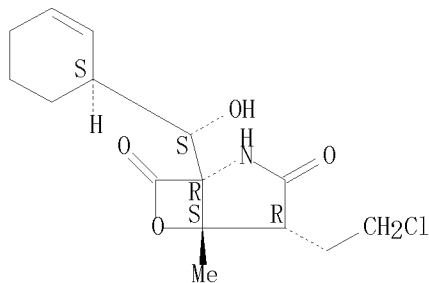
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combination of novel proteasome inhibitor NPI-0052 and lenalidomide trigger in vitro and in vivo synergistic cytotoxicity in multiple myeloma)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 33 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:150430 CAPLUS  
DOCUMENT NUMBER: 152:231208  
TITLE: Accelerated therapy  
INVENTOR(S): McCulloch, William; Prince, Henry Miles  
PATENT ASSIGNEE(S): Gloucester Pharmaceuticals, Inc., USA; Peter MacCallum  
Cancer Centre  
SOURCE: PCT Int. Appl., 43pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010014819	A1	20100204	WO 2009-US52269	20090730
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
US 20100152100	A1	20100617	US 2009-512419	20090730
PRIORITY APPLN. INFO.:			US 2008-84797P	P 20080730

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

ABSTRACT:

The invention encompasses the surprising finding that romidepsin can safely be administered to humans on an accelerated dosing schedule.

IT **437742-34-2**, Salinosporamide A

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

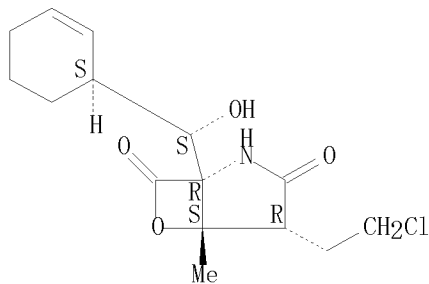
(Biological study); USES (Uses)

(codrug; accelerated romidepsin dosing therapy of neoplasm and other proliferative diseases)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 34 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2010:79071 CAPLUS

DOCUMENT NUMBER: 152:309874

TITLE: Engineering Fluorometabolite Production: Fluorinase  
Expression in *Salinispora tropica* Yields  
Fluorosalinoporamide

AUTHOR(S): Eustaquio, Alessandra S.; O'Hagan, David; Moore,  
Bradley S.

CORPORATE SOURCE: Scripps Institution of Oceanography and Skaggs School  
of Pharmacy and Pharmaceutical Sciences, University of  
California at San Diego, La Jolla, CA, 92093-0204, USA

SOURCE: Journal of Natural Products (2010), 73(3), 378-382

CODEN: JNPRDF; ISSN: 0163-3864

PUBLISHER: American Chemical Society-American Society of  
Pharmacognosy

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Organofluorine compds. play an important role in medicinal chemical, where they are responsible for up to 15% of the pharmaceutical products on the market. While natural products are valuable sources of new chemical entities, natural fluorinated mols. are extremely rare and the pharmaceutical industry has not benefited from a microbial source of this class of compds. *Streptomyces cattleya* is an unusual bacterium in that it elaborates fluoroacetate and the amino acid 4-fluorothreonine. The discovery in 2002 of the fluorination enzyme FlA responsible for C-F bond formation in *S. cattleya*, and its subsequent characterization, opened up for the first time the prospect of genetically engineering fluorometabolite production from fluoride ion in host organisms. As a proof of principle, we report here the induced production of fluorosalinoporamide by replacing the chlorinase gene *sall* from *Salinispora tropica* with the fluorinase gene *flA*.

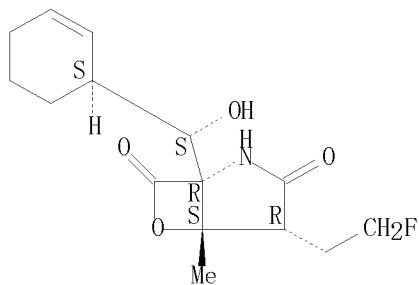
IT **889457-14-1P**, Fluorosalinoporamide

RL: BMF (Bioindustrial manufacture); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)  
(fluorinase expression in *Salinispora tropica* yields  
fluorosalinoporamide)

RN 889457-14-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-fluoroethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



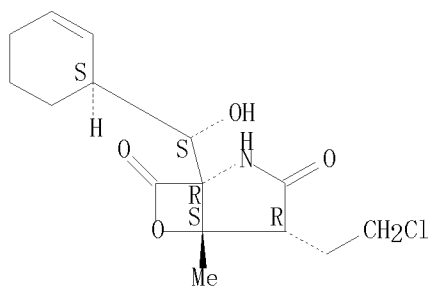
IT **437742-34-2P**, Salinoporamide A

RL: BYP (Byproduct); PREP (Preparation)  
(fluorinase expression in *Salinispora tropica* yields  
fluorosalinoporamide)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	4	THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT:	28	THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 35 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:62762 CAPLUS  
DOCUMENT NUMBER: 153:162883  
TITLE: The development and pharmacology of proteasome  
inhibitors for the management and treatment of cancer  
AUTHOR(S): Ruggeri, Bruce; Miknyoczki, Sheila; Dorsey, Bruce;  
Hui, Ai-Min  
CORPORATE SOURCE: Discovery Research, Cephalon, Inc., West Chester, PA,  
19380, USA  
SOURCE: Advances in Pharmacology (San Diego, CA, United  
States) (2009), 57(Contemporary Aspects of Biomedical  
Research: Drug Discovery), 91-135  
CODEN: ADPHEL; ISSN: 1054-3589  
PUBLISHER: Elsevier Inc.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

A review. The ubiquitin-proteasome complex is an important mol. target for the design of novel chemotherapeutics. This complex plays a critical role in signal transduction pathways important for tumor cell growth and survival, cell-cycle control, transcriptional regulation, and the modulation of cellular stress responses to endogenous and exogenous stimuli. The sensitivity of transformed cells to proteasome inhibitors and the successful design of treatment protocols with tolerable, albeit narrow, therapeutic indexes have made proteasome inhibition a viable strategy for cancer treatment. Clin. validation of the proteasome as a mol. target was achieved with the approval of bortezomib, a boronic acid proteasome inhibitor, for the treatment of multiple myeloma and mantle cell lymphoma. Several "next-generation" proteasome inhibitors (carfilzomib and PR-047, NPI-0052, and CEP-18770) representing distinct structural classes (peptidyl epoxyketones,  $\beta$ -lactones, and peptidyl boronic acids, resp.), mechanisms of action, pharmacol. and pharmacodynamic activity profiles, and therapeutic indexes have now entered clin. development. These agents may expand the clin. utility of proteasome inhibitors for the treatment of solid tumors and for specific non-oncol., i.e., inflammatory disease, indications as well. This chapter addresses the biol. of the proteasome, the medicinal chemical and mechanisms of action of proteasome inhibitors currently in clin. development, the preclin. and clin. pharmacol. and safety profiles of bortezomib and the newer compds. against hematol. and solid tumors. Future directions for research and other applications for this novel class of therapeutics agents are considered in this chapter.

IT 437742-34-2, NPI-0052

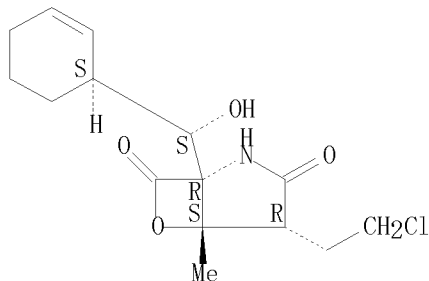
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)

(development of proteasome inhibitors like NPI-0052 with favorable  
pharmacol. may be effective for management and treatment of patient  
with cancer)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
(1 CITINGS)  
REFERENCE COUNT: 155 THERE ARE 155 CITED REFERENCES AVAILABLE FOR  
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT



L6 ANSWER 36 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2010:23408 CAPLUS

DOCUMENT NUMBER: 153:134015

TITLE: From natural products to clinical trials: NPI-0052 (salinosporamide A), a marine actinomycete-derived anticancer agent

AUTHOR(S): Lam, Kin S.; Lloyd, G. Kenneth; Neuteboom, Saskia T. C.; Palladino, Michael A.; Sethna, Kobi M.; Spear, Matthew A.; Potts, Barbara C.

CORPORATE SOURCE: Nereus Pharmaceuticals, Inc, San Diego, CA, 92121, USA

SOURCE: Natural Product Chemistry for Drug Discovery (2010), 355-373. Editor(s): Buss, Antony D.; Butler, Mark S. Royal Society of Chemistry: Cambridge, UK.

CODEN: 69MGLO; ISBN: 978-0-85404-193-0

DOCUMENT TYPE: Conference; General Review

LANGUAGE: English

ABSTRACT:

A review. The unique aspects of developing a marine actinomycete-derived therapeutic agent, NPI-0052, are highlighted. Salinosporamide A (designated as NPI-0052) was first isolated from the fermentation broth of *Salinispora tropica* strain CNB392. This highly potent 20S proteasome inhibitor is currently undergoing Phase I clin. studies for the treatment of various hematol. and solid tumor malignancies. An account is given of events from the early mechanism of action and preclin. studies that supported its entry into clin. trials in cancer patients, to the current strategy for its continued development as an anticancer agent.

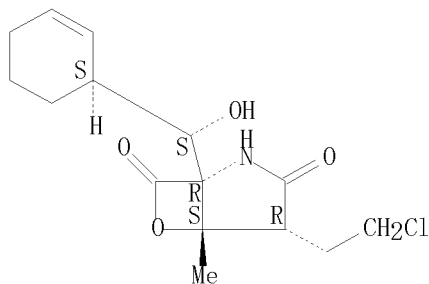
IT **437742-34-2**, Salinosporamide A

RL: NPO (Natural product occurrence); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses) (marine *S. tropica*-derived protease inhibitor salinosporamide A that overcame challenge of developing compound with labile  $\beta$ -lactone ring, chloroethyl was useful as anticancer agent for patient and in validating drug discovery, development)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

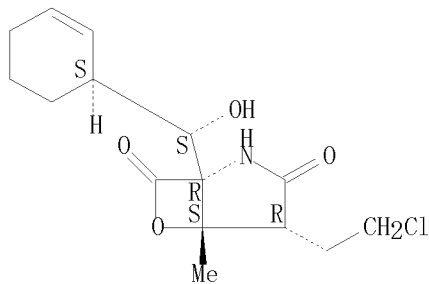
REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 37 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2010:23407 CAPLUS  
DOCUMENT NUMBER: 153:134014  
TITLE: A snapshot of natural product-derived compounds in late stage clinical development at the end of 2008  
AUTHOR(S): Butler, Mark S.  
CORPORATE SOURCE: MerLion Pharmaceuticals, Singapore, 117528, Singapore  
SOURCE: Natural Product Chemistry for Drug Discovery (2010), 321-354. Editor(s): Buss, Antony D.; Butler, Mark S. Royal Society of Chemistry: Cambridge, UK. CODEN: 69MGLO; ISBN: 978-0-85404-193-0  
DOCUMENT TYPE: Conference; General Review  
LANGUAGE: English  
ABSTRACT:

A review. A snapshot of natural product (NP)-derived drug development at the end of 2008 with NP-derived drugs launched since 2003 and NP-derived compds. that are undergoing late stage clin. evaluation is provided. Compds. are classified into three groups: NPs, semi-synthetic NPs and NP-derived.

IT **437742-34-2**, Salinosporamide A  
RL: NPO (Natural product occurrence); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses) (natural product-derived compound salinosporamide A in late stage development may be effective in patient with cancer)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 286 THERE ARE 286 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L6 ANSWER 38 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:1566750 CAPLUS  
DOCUMENT NUMBER: 152:67621  
TITLE:  $\beta$ -Adrenergic receptor agonists for the treatment  
of B-cell proliferative disorders  
INVENTOR(S): Rickles, Richard; Lee, Margaret S.  
PATENT ASSIGNEE(S): CombinatoRx, Inc., USA  
SOURCE: PCT Int. Appl., 111 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009151569	A2	20091217	WO 2009-US3449	20090608
WO 2009151569	A3	20100225		
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
US 20100009934	A1	20100114	US 2009-480034	20090608
PRIORITY APPLN. INFO.:			US 2008-60064P	P 20080609

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

## ABSTRACT:

The invention discloses a method for treating a B-cell proliferative disorder by administering to a patient a  $\beta$ -Adrenergic receptor (BAR) agonist, e.g., formulated for administration by a route other than inhalation (such as for oral or i.v. administration), in an amount effective to treat the B-cell proliferative disorder. The BAR agonist may be administered as a monotherapy or in combination with one or more other agents, e.g., a PDE inhibitor, an A2A receptor agonist, or an antiproliferative compound, in amts. that together are effective to treat the B-cell proliferative disorder. The invention further discloses pharmaceutical compns. and kits including a BAR agonist, alone or in combination with addnl. agents, for the treatment of a B-cell proliferative disorder.

IT 437742-34-2, NPI 0052

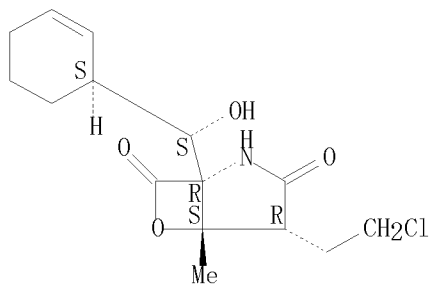
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

( $\beta$ -Adrenergic receptor agonists for treatment of B-cell proliferative disorders, and use with other agents)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).







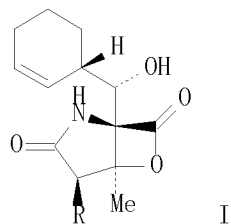
L6 ANSWER 39 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:1437181 CAPLUS  
 DOCUMENT NUMBER: 151:550345  
 TITLE: Salinosporamide derivatives as proteasome inhibitors  
 INVENTOR(S): Macherla, Venkat Rami Reddy; Potts, Barbara Christine;  
 Manam, Rama Rao; Mearthur, Katherine A.; Chao,  
 Ta-Hsiang; Neuteboom, Saskia Theodora Cornelia  
 PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
 SOURCE: PCT Int. Appl., 144pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009140287	A1	20091119	WO 2009-US43644	20090512
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM AU 2009246467 A1 20091119 AU 2009-246467 20090512 CA 2723465 A1 20091119 CA 2009-2723465 20090512 US 20090298906 A1 20091203 US 2009-464686 20090512 EP 2276765 A1 20110126 EP 2009-747371 20090512 R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS KR 2011011645 A 20110208 KR 2010-7026654 20090512 PRIORITY APPLN. INFO.: US 2008-52576P P 20080512 WO 2009-US43644 W 20090512				

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 151:550345; MARPAT 151:550345

GRAPHIC IMAGE:



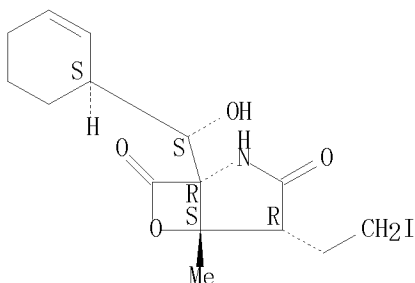
#### ABSTRACT:

Derivs., such as I [R = (CH<sub>2</sub>)<sub>n</sub>R<sub>1</sub>; R<sub>1</sub> = H, OH, halogen, alkylsulfonyloxy, arylsulfonyloxy, acyloxy, alkyloxy, etc.; n = 1, 2, 3], of the fused  $\gamma$ -lactam- $\beta$ -lactone salinosporamide A I [R = (CH<sub>2</sub>)<sub>2</sub>Cl] were prepared for use in pharmaceutical compns. as proteasome inhibitors for treating, alleviating or diagnosing a neoplastic disease, microbial disease and inflammation. Thus, salinosporamide A hydroxy derivative I [R = (CH<sub>2</sub>)<sub>2</sub>OH] was prepared with 35% yield by treating salinosporamide A with AgF supported on CaF<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> at 40° for 18 h. Subsequently, the salinosporamide A sulfonate derivative I [R = (CH<sub>2</sub>)<sub>2</sub>OSO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-4-Ph] as prepared with 26% yield via an esterification reaction of the hydroxy derivative with Ph-4-C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>Cl using NEt<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> at rt for 18 h. The prepared salinosporamide A derivs. were evaluated for inhibition of the CT-L, T-L and C-L activities of rabbit 20S proteasome, for in vitro cytotoxicity against the NCI panel of 60 human tumor cell lines, for anti-inflammatory activity by inhibition of NF- $\kappa$ B-mediated luciferase

activity and for antimicrobial activity.

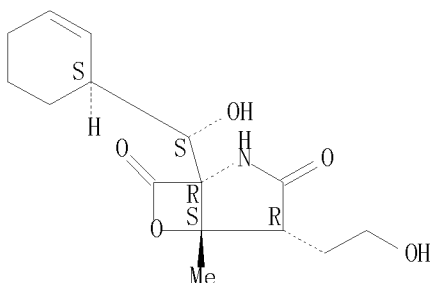
IT 823229-34-1P 823229-54-5P  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (preparation of salinosporamide derivs. for therapeutic use as proteasome inhibitors for the treatment of cancer, microbial disease or inflammation)  
 RN 823229-34-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



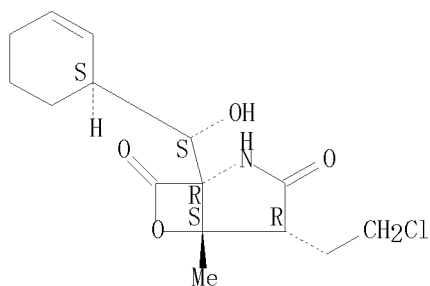
RN 823229-54-5 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



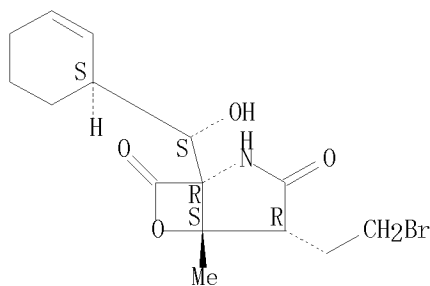
IT 437742-34-2, Salinosporamide A 872360-15-1  
 RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use);  
 BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)  
 (preparation of salinosporamide derivs. for therapeutic use as proteasome inhibitors for the treatment of cancer, microbial disease or inflammation)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 872360-15-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



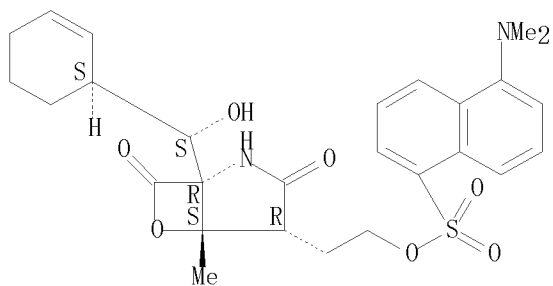
IT 1073241-49-2P      1196454-69-9P      1196454-70-2P  
1196454-71-3P      1196454-72-4P      1196454-73-5P  
1196454-74-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
 (Uses)

(preparation of salinosporamide derivs. for therapeutic use as proteasome  
 inhibitors for the treatment of cancer, microbial disease or  
 inflammation)

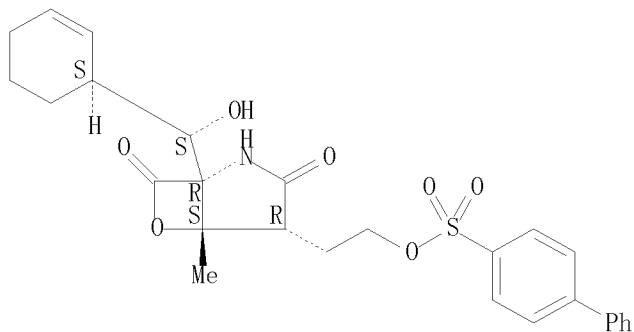
RN 1073241-49-2 CAPLUS  
 CN 1-Naphthalenesulfonic acid, 5-(dimethylamino)-,  
 2-[(1R,4R,5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-  
 dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA INDEX NAME)

Absolute stereochemistry.



RN 1196454-69-9 CAPLUS  
 CN [1,1'-Biphenyl]-4-sulfonic acid, 2-[(1R,4R,5S)-1-[(S)-(1S)-2-cyclohexen-1-  
 ylhydroxymethyl]-5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-  
 yl]ethyl ester (CA INDEX NAME)

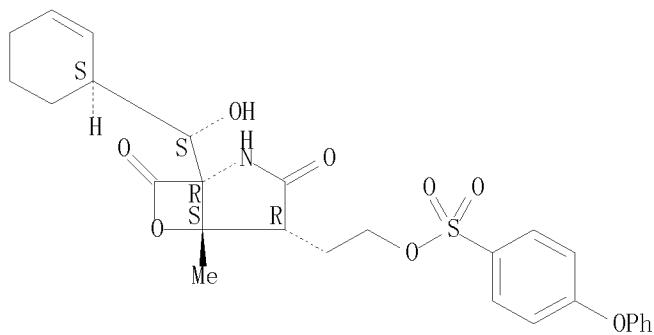
Absolute stereochemistry.



RN 1196454-70-2 CAPLUS

CN Benzenesulfonic acid, 4-phenoxy-, 2-[(1R, 4R, 5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3, 7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA INDEX NAME)

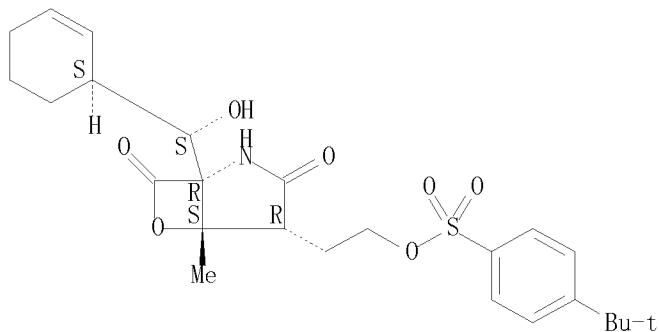
Absolute stereochemistry.



RN 1196454-71-3 CAPLUS

CN Benzenesulfonic acid, 4-(1,1-dimethylethyl)-, 2-[(1R, 4R, 5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3, 7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA INDEX NAME)

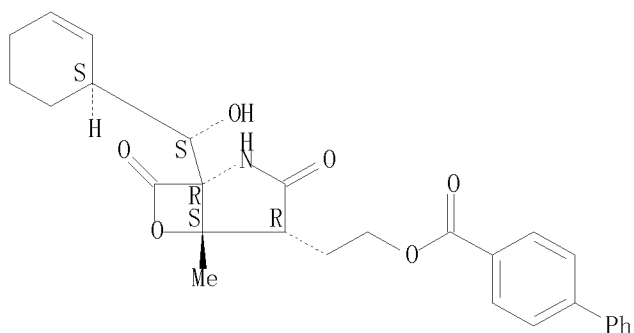
Absolute stereochemistry.



RN 1196454-72-4 CAPLUS

CN [1,1'-Biphenyl]-4-carboxylic acid, 2-[(1R, 4R, 5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3, 7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA INDEX NAME)

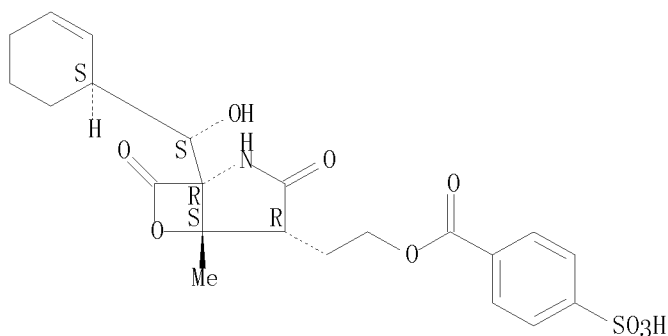
Absolute stereochemistry.



RN 1196454-73-5 CAPLUS

CN Benzoic acid, 4-sulfo-, 1-[2-[(1R,4R,5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl] ester (CA INDEX NAME)

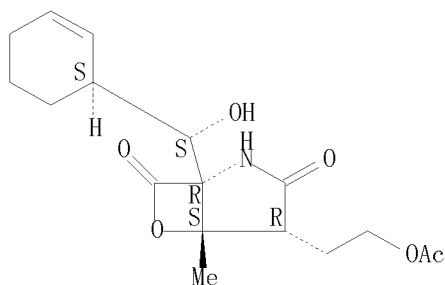
Absolute stereochemistry.



RN 1196454-74-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-[2-(acetoxylethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 823229-26-1 863126-95-8 872360-24-2  
889457-14-1 1057246-23-7 1073241-43-6

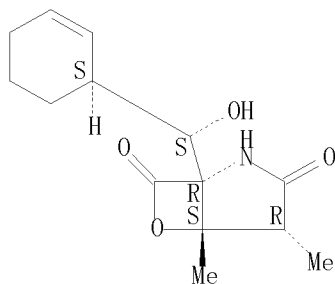
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of salinosporamide derivs. for therapeutic use as proteasome inhibitors for the treatment of cancer, microbial disease or inflammation)

RN 823229-26-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4R,5S)- (CA INDEX NAME)

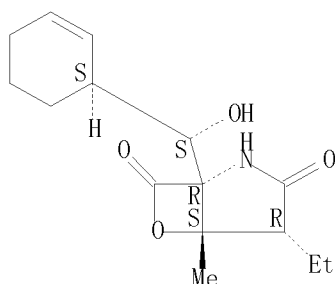
Absolute stereochemistry.



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

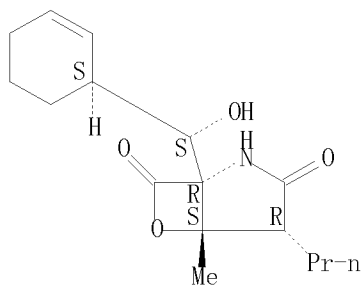
Absolute stereochemistry. Rotation (-).



RN 872360-24-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-,  
(1R,4R,5S)- (CA INDEX NAME)

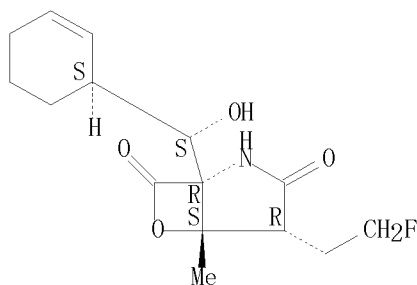
Absolute stereochemistry.



RN 889457-14-1 CAPLUS

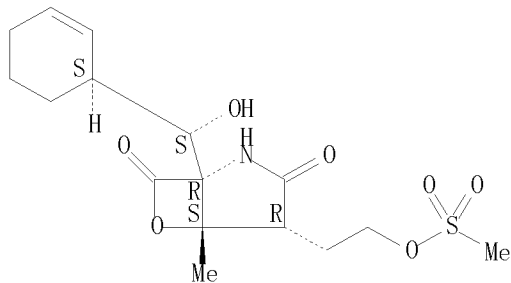
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-fluoroethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



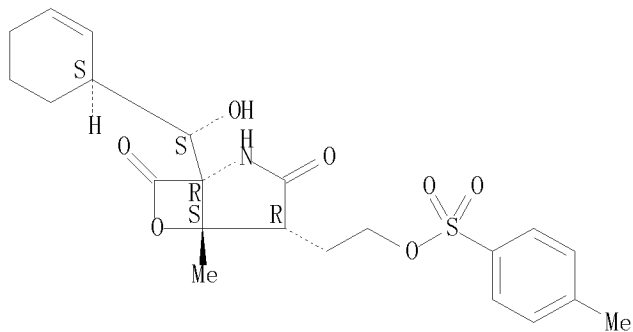
RN 1057246-23-7 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-  
[(methylsulfonyl)oxy]ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1073241-43-6 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-[[4-  
methylphenyl)sulfonyl]oxy]ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 40 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:1436843 CAPLUS  
DOCUMENT NUMBER: 151:565117  
TITLE: Use of salinosporamide A to inhibit metastasis  
INVENTOR(S): Baritaki, Stavroula; Bonavida, Benjamin; Palladino, Michael  
PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
SOURCE: U.S. Pat. Appl. Publ., 41pp.  
CODEN: USXXCO  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20090285836	A1	20091119	US 2009-423713	20090414
PRIORITY APPLN. INFO.:			US 2008-44861P	P 20080414
			US 2008-57631P	P 20080530

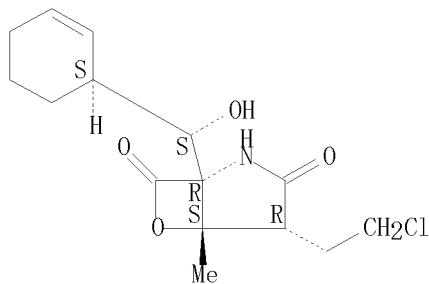
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

ABSTRACT:

The present invention relates to methods and compns. for treating and evaluating metastatic conditions. A method for inhibiting metastasis in a subject comprises identifying a subject experiencing or at risk for metastasis and administering to the subject an effective amount of salinosporamide A (NPI-0052), or a pharmaceutically acceptable salt or pro-drug ester thereof, optionally in combination with an effective amount of an addnl. anticancer agent. Thus, NPI-0052 sensitized tumor cells to chemo- and TRAIL-mediated apoptosis via direct inhibition of NF- $\kappa$ B. NPI-0052 induced RKIP expression which acted as an addnl. inhibitor of NF- $\kappa$ B. RKIP is directly involved in tumor cell sensitivity to chemotherapeutic drugs or TRAIL. NF- $\kappa$ B inhibition by NPI-0052 and/or by NPI-0052-induced RKIP upregulation resulted in inhibition of antiapoptotic gene products and inhibition of YY1 resulting in induction of DR5 and sensitization to TRAIL. Overexpression of RKIP by NPI-0052 was reversely correlated with SNAIL downregulation and inhibition of epithelial mesenchymal transition (EMT)-inducing gene products (e.g. vimentin, fibronectin) resulting in inhibition of metastasis.

IT 437742-34-2, Salinosporamide A  
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(salinosporamide A inhibition of metastasis and evaluation of metastatic potential)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).





L6 ANSWER 41 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2009:1338186 CAPLUS

DOCUMENT NUMBER: 152:111031

TITLE: Proteasome inhibitors activate autophagy as a cytoprotective response in human prostate cancer cells

AUTHOR(S): Zhu, K.; Dunner, K.; McConkey, D. J.

CORPORATE SOURCE: Department of Cancer Biology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

SOURCE: Oncogene (2010), 29(3), 451-462

CODEN: ONCNES; ISSN: 0950-9232

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

The ubiquitin-proteasome and lysosome-autophagy pathways are the two major intracellular protein degradation systems that work cooperatively to maintain homeostasis. Proteasome inhibitors (PIs) have clin. activity in hematol. tumors, and inhibitors of autophagy are also being evaluated as potential antitumor therapies. In this study, we found that chemical PIs and small interfering RNA-mediated knockdown of the proteasome's enzymic subunits promoted autophagosome formation, stimulated autophagic flux, and upregulated expression of the autophagy-specific genes (ATGs) (ATG5 and ATG7) in some human prostate cancer cells and immortalized mouse embryonic fibroblasts (MEFs). Upregulation of ATG5 and ATG7 only occurred in cells displaying PI-induced phosphorylation of the eukaryotic translation initiation factor 2 alpha (eIF2 $\alpha$ ), an important component of the unfolded protein responses. Furthermore, PIs did not induce autophagy or upregulate ATG5 in MEFs expressing a phosphorylation-deficient mutant form of eIF2 $\alpha$ . Combined inhibition of autophagy and the proteasome induced an accumulation of intracellular protein aggregates reminiscent of neuronal inclusion bodies and caused more cancer cell death than blocking either degradation pathway alone. Overall, our data show that proteasome inhibition activates autophagy through a phospho-eIF2 $\alpha$ -dependent mechanism to eliminate protein aggregates and alleviate proteotoxic stress.

IT 437742-34-2, NPI-0052

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

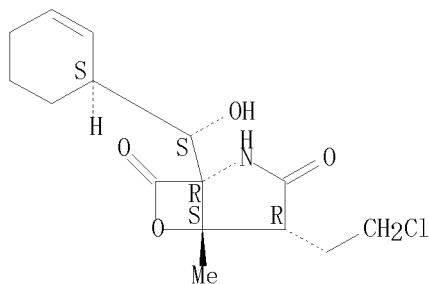
(proteasome inhibitors activate autophagy as cytoprotective response in human prostate cancer cells)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,

4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 42 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2009:1324442 CAPLUS

DOCUMENT NUMBER: 152:66820

TITLE: Pivotal Roles of Snail Inhibition and RKIP Induction  
by the Proteasome Inhibitor NPI-0052 in Tumor Cell  
Chemoimmunosensitization

AUTHOR(S): Baritaki, Stavroula; Yeung, Kam; Palladino, Michael;  
Berenson, James; Bonavida, Benjamin

CORPORATE SOURCE: Department of Microbiology, Immunology and Molecular  
Genetics, Jonsson Comprehensive Cancer Center, David  
Geffen School of Medicine, University of California at  
Los Angeles, Los Angeles, CA, USA

SOURCE: Cancer Research (2009), 69(21), 8376-8385

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

The novel proteasome inhibitor NPI-0052 has been shown to sensitize tumor cells to apoptosis by various chemotherapeutic drugs and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), although the mechanisms involved are not clear. We hypothesized that NPI-0052-mediated sensitization may result from NF- $\kappa$ B inhibition and downstream modulation of the metastasis inducer Snail and the metastasis suppressor/immunosurveillance cancer gene product Raf-1 kinase inhibitory protein (RKIP). Human prostate cancer cell lines were used as models, as they express different levels of these proteins. We show that NPI-0052 inhibits both NF- $\kappa$ B and Snail and induces RKIP expression, thus resulting in cell sensitization to CDDP and TRAIL. The direct role of NF- $\kappa$ B inhibition in sensitization was corroborated with the NF- $\kappa$ B inhibitor DHMEQ, which mimicked NPI-0052 in sensitization and inhibition of Snail and induction of RKIP. The direct role of Snail inhibition by NPI-0052 in sensitization was shown with Snail small interfering RNA, which reversed resistance and induced RKIP. Likewise, the direct role of RKIP induction in sensitization was revealed by both overexpression of RKIP (mimicking NPI-0052) and RKIP small interfering RNA that inhibited NPI-0052-mediated sensitization. These findings show that NPI-0052 modifies the NF- $\kappa$ B-Snail-RKIP circuitry in tumor cells and results in downstream inhibition of antiapoptotic gene products and chemoimmunosensitization. The findings also identified Snail and RKIP as targets for reversal of resistance. [Cancer Res 2009;69(21):8376-85].

IT 437742-34-2, NPI-0052

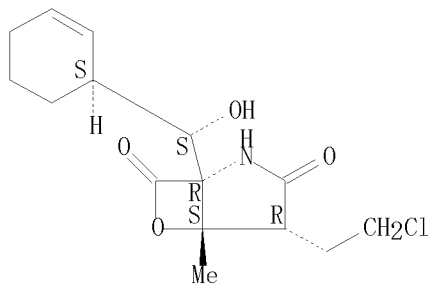
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pivotal roles of snail inhibition and RKIP induction by proteasome inhibitor NPI-0052 in tumor cell chemoimmunosensitization)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 43 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:1217198 CAPLUS  
DOCUMENT NUMBER: 151:571268  
TITLE: Formal synthesis of salinosporamide A starting from D-glucose  
AUTHOR(S): Momose, Takayuki; Kaiya, Yuji; Hasegawa, Jun-ichi; Sato, Takaaki; Chida, Noritaka  
CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama, 223-8522, Japan  
SOURCE: Synthesis (2009), (17), 2983-2991  
CODEN: SYNTBF; ISSN: 0039-7881  
PUBLISHER: Georg Thieme Verlag  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
OTHER SOURCE(S): CASREACT 151:571268  
ABSTRACT:

A formal synthesis of salinosporamide A is described. The tertiary alc. function in salinosporamide A was stereoselectively generated via the substrate control by the reaction of a cyclic ketone derived from D-glucose with Me<sub>3</sub>Al, and subsequent Overman rearrangement of an allylic trichloroacetimidate effectively constructed the tetrasubstituted carbon with nitrogen. Formation of  $\gamma$ -lactam, followed by the introduction of a cyclohexenyl unit furnished the Corey's intermediate of salinosporamide A.

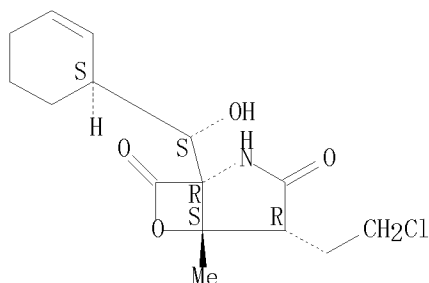
IT **437742-34-2P**

RL: SPN (Synthetic preparation); PREP (Preparation)  
(synthesis of salinosporamide A starting from D-glucose via Overman rearrangement of a glycosyl allylic alc.)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)  
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 44 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2009:1152995 CAPLUS

DOCUMENT NUMBER: 152:161782

TITLE: Genomic islands link secondary metabolism to functional adaptation in marine Actinobacteria

AUTHOR(S): Penn, Kevin; Jenkins, Caroline; Nett, Markus; Udway, Daniel W.; Gontang, Erin A.; McGlinchey, Ryan P.; Foster, Brian; Lapidus, Alla; Podell, Sheila; Allen, Eric E.; Moore, Bradley S.; Jensen, Paul R.

CORPORATE SOURCE: Center for Marine Biotechnology and Biomedicine, Scripps Institution of Oceanography, University of California San Diego, La Jolla, CA, USA

SOURCE: ISME Journal (2009), 3(10), 1193-1203

CODEN: IJSOCF; ISSN: 1751-7362

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

## ABSTRACT:

Genomic islands have been shown to harbor functional traits that differentiate ecol. distinct populations of environmental bacteria. A comparative anal. of the complete genome sequences of the marine Actinobacteria *Salinispora tropica* and *Salinispora arenicola* reveals that 75% of the species-specific genes are located in 21 genomic islands. These islands are enriched in genes associated with secondary metabolite biosynthesis providing evidence that secondary metabolism is linked to functional adaptation. Secondary metabolism accounts for 8.8% and 10.9% of the genes in the *S. tropica* and *S. arenicola* genomes, resp., and represents the major functional category of annotated genes that differentiates the 2 species. Genomic islands harbor all 25 of the species-specific biosynthetic pathways, the majority of which occur in *S. arenicola* and may contribute to the cosmopolitan distribution of this species. Genome evolution is dominated by gene duplication and acquisition, which in the case of secondary metabolism provide immediate opportunities for the production of new bioactive products. Evidence that secondary metabolic pathways are exchanged horizontally, coupled with earlier evidence for fixation among globally distributed populations, supports a functional role and suggests that the acquisition of natural product biosynthetic gene clusters represents a previously unrecognized force driving bacterial diversification. Species-specific differences observed in clustered regularly interspaced short palindromic repeat sequences suggest that *S. arenicola* may possess a higher level of phage immunity, whereas a highly duplicated family of polymorphic membrane proteins provides evidence for a new mechanism of marine adaptation in Gram-pos. bacteria. The complete, annotated genomes of *S. tropica* strain CBN-440 and *S. arenicola* strain CNS-205 are deposited in GenBank/EMBL/DDBJ with accession nos. CP000667 and CP000850, resp.

IT 437742-34-2, Salinosporamide A

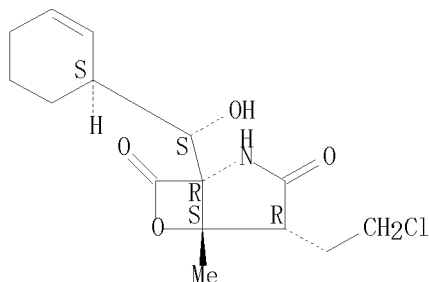
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(gene cluster for biosynthesis of; genomic islands link secondary metabolism to functional adaptation in marine Actinobacteria)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 45 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:1137565 CAPLUS  
DOCUMENT NUMBER: 151:381091  
TITLE: Total synthesis of salinosporamide A and analogs thereof  
INVENTOR(S): Ling, Taotao; Danishefsky, Samuel  
PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
SOURCE: U.S. Pat. Appl. Publ., 128pp.  
CODEN: USXXCO  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20090234137	A1	20090917	US 2009-399382	20090306
AU 2009241635	A1	20091105	AU 2009-241635	20090306
CA 2717715	A1	20091105	CA 2009-2717715	20090306
WO 2009134531	A2	20091105	WO 2009-US36376	20090306
WO 2009134531	A3	20101118		
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
KR 2010131475	A	20101215	KR 2010-7022279	20090306
EP 2262812	A2	20101222	EP 2009-739333	20090306
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS			
MX 201009860	A	20100930	MX 2010-9860	20100906
PRIORITY APPLN. INFO. :			US 2008-34900P	P 20080307
			US 2008-73545P	P 20080618
			WO 2009-US36376	W 20090306
OTHER SOURCE(S):	CASREACT 151:381091; MARPAT 151:381091			
GRAPHIC IMAGE:				

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

#### ABSTRACT:

The present application relates to certain compds. and to methods for the preparation of certain compds. that can be used in the fields of chemical and medicine. Specifically, described herein are methods for the preparation of various compds. and intermediates, and the compds. and intermediates themselves. More specifically, described herein are methods for synthesizing Salinosporamide A (I) and its analogs that includes forming a compound II [R1 = H, (un)substituted C1-6-alkyl, (un)substituted aryl; R2 = H, (un)substituted C1-6-alkyl, (un)substituted aryl, (un)substituted arylalkyl]. The chemical synthesis comprises: (a) oxidizing oxazabicyclooctene III [R3 = (un)substituted C1-24-alkyl, (un)substituted C1-24-alkenyl, (un)substituted C1-24-alkynyl, (un)substituted aryl, (un)substituted heteroaryl, (un)substituted C3-24-cycloalkyl, (un)substituted C3-24-cycloalkenyl, (un)substituted C3-24-cycloalkynyl, (un)substituted aryl(C1-6-alkyl), (un)substituted heteroaryl(C1-6-alkyl)] to epoxide IV; and, (b) cleavage of IV to form diol V. The chemical synthesis further comprises: (a) oxidizing R3 in oxazabicyclooctenone VI [R3 = CH2CH:CHR5, CH2C.tplbond.CR5, CH2Ar, CH2Het; R5 = H, (un)substituted C1-24-alkyl, (un)substituted C1-24-alkenyl, (un)substituted C1-24-alkynyl, (un)substituted aryl, (un)substituted heteroaryl, (un)substituted C3-24-cycloalkyl, (un)substituted C3-24-cycloalkenyl, (un)substituted C3-24-cycloalkynyl, (un)substituted aryl(C1-6-alkyl), (un)substituted heteroaryl(C1-6-alkyl); Ar = (un)substituted aryl; Het = (un)substituted

heteroaryl] to an aldehyde and further reducing the aldehyde to alc. VII; (b) oxidizing VII to II; and, (c) cleaving II to keto diol VIII.

IT **437742-34-2P**, Salinosporamide A

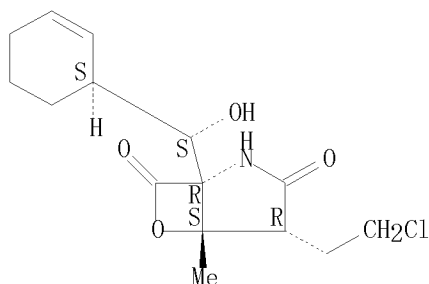
RL: SPN (Synthetic preparation); PREP (Preparation)

(analog; total synthesis of salinosporamide A and analogs thereof)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **1057246-23-7P** **1073241-43-6P**

RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP

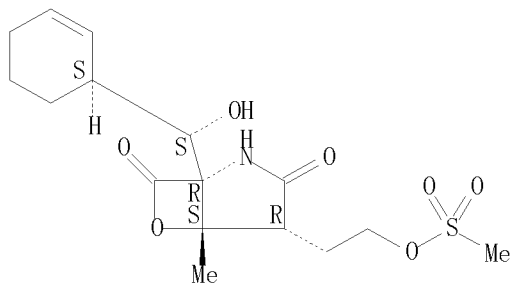
(Preparation); RACT (Reactant or reagent)

(preparation and chlorination of; total synthesis of salinosporamide A and analogs thereof)

RN 1057246-23-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-  
[(methylsulfonyl)oxy]ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

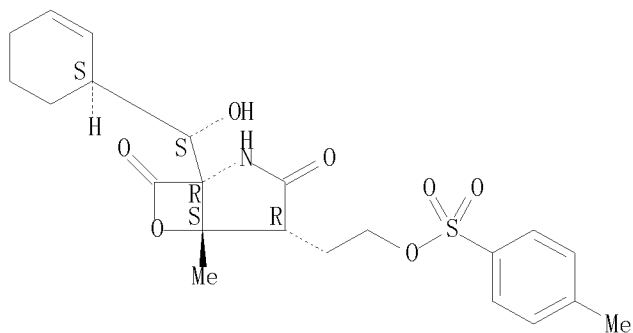
Absolute stereochemistry.



RN 1073241-43-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-[[4-  
methylphenyl)sulfonyl]oxy]ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

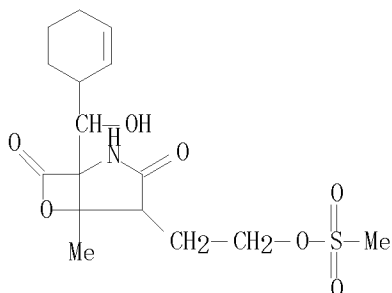


IT 1187528-79-5P 1187528-80-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation and chlorination of; total synthesis of salinosporamide A and analogs thereof)

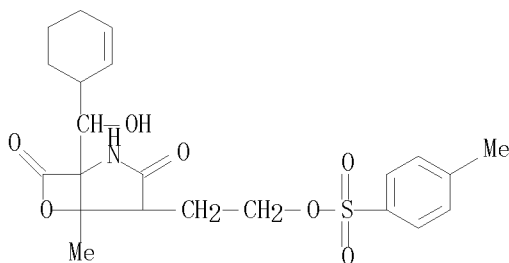
RN 1187528-79-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(2-cyclohexen-1-ylhydroxymethyl)-5-methyl-4-[2-  
[(methylsulfonyl)oxy]ethyl]- (CA INDEX NAME)



RN 1187528-80-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(2-cyclohexen-1-ylhydroxymethyl)-5-methyl-4-[2-[(4-  
methylphenyl)sulfonyl]oxy]ethyl]- (CA INDEX NAME)



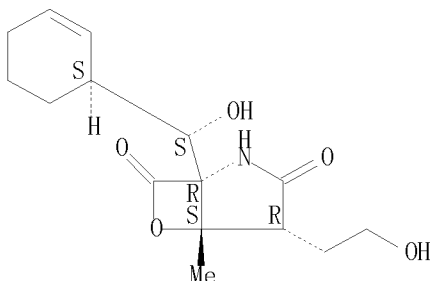
IT 823229-54-5P

RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation and mesylation or tosylation of; total synthesis of salinosporamide A and analogs thereof)

RN 823229-54-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



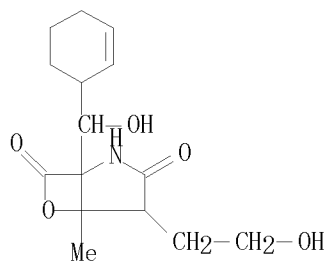
IT 1187528-63-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(total synthesis of salinosporamide A and analogs thereof)



RN 1187528-63-7 CAPLUS

CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(2-cyclohexen-1-ylhydroxymethyl)-4-(2-hydroxyethyl)-5-methyl- (CA INDEX  
NAME)

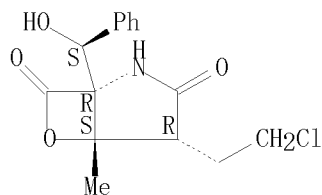


L6 ANSWER 46 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:1119601 CAPLUS  
 DOCUMENT NUMBER: 151:356678  
 TITLE: Function-Oriented Biosynthesis of  $\beta$ -Lactone  
 Proteasome Inhibitors in *Salinispora tropica*  
 AUTHOR(S): Nett, Markus; Gulder, Tobias A. M.; Kale, Andrew J.;  
 Hughes, Chambers C.; Moore, Bradley S.  
 CORPORATE SOURCE: Scripps Institution of Oceanography and the Skaggs  
 School of Pharmacy and Pharmaceutical Sciences,  
 University of California at San Diego, La Jolla, CA,  
 92093, USA  
 SOURCE: Journal of Medicinal Chemistry (2009), 52(19),  
 6163-6167  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 ABSTRACT:

The natural proteasome inhibitor salinosporamide A from the marine bacterium *Salinispora tropica* is a promising drug candidate for the treatment of multiple myeloma and mantle cell lymphoma. Using a comprehensive approach that combined chemical synthesis with metabolic engineering, we generated a series of salinosporamide analogs with altered proteasome binding affinity. One of the engineered compds. is equipotent to salinosporamide A in inhibition of the chymotrypsin-like activity of the proteasome yet exhibits superior activity in the cell-based HCT-116 assay.

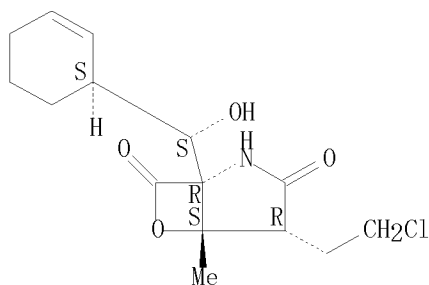
IT 1044999-00-9P, Salinosporamide X 4  
 RL: BMF (Bioindustrial manufacture); BSU (Biological study, unclassified);  
 PRP (Properties); PUR (Purification or recovery); BIOL (Biological study);  
 PREP (Preparation)  
 (function-oriented biosynthesis of  $\beta$ -lactone proteasome inhibitors  
 in *Salinispora tropica*)  
 RN 1044999-00-9 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA  
 INDEX NAME)

Absolute stereochemistry.



IT 437742-34-2, Salinosporamide A  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (function-oriented biosynthesis of  $\beta$ -lactone proteasome inhibitors  
 in *Salinispora tropica*)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	7	THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT:	29	THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 47 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:1112038 CAPLUS  
 DOCUMENT NUMBER: 151:334895  
 TITLE: Anti-human TRAIL receptor TR4 antibodies and scFvs for  
 diagnosis and treatment of cancer or  
 hyperproliferative disease  
 INVENTOR(S): Salcedo, Theodora W.; Ruben, Steven M.; Rosen, Craig  
 A.; Albert, Vivian R.; Dobson, Claire; Vaughan,  
 Tristan  
 PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA  
 SOURCE: U.S. Pat. Appl. Publ., 153pp., Cont.-in-part of U.S.  
 Ser. No. 391,384.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 15  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20090226429	A1	20090910	US 2008-16372	20080118
US 20030190685	A1	20031009	US 2002-139785	20020507
US 7064189	B2	20060620		
WO 2004016753	A2	20040226	WO 2003-US25457	20030815
WO 2004016753	A3	20040617		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,				
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,				
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,				
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,				
TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,				
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,				
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,				
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20050129699	A1	20050616	US 2004-986047	20041112
US 7348003	B2	20080325		
US 20050214209	A1	20050929	US 2004-986349	20041112
US 20060270837	A1	20061130	US 2006-391384	20060329
US 7361341	B2	20080422		
AU 2008201237	A1	20080410	AU 2008-201237	20080314
JP 2009062393	A	20090326	JP 2008-291575	20081113
PRIORITY APPLN. INFO. :			US 2001-293473P	P 20010525
			US 2001-294981P	P 20010604
			US 2001-309176P	P 20010802
			US 2001-323807P	P 20010921
			US 2001-327364P	P 20011009
			US 2001-331044P	P 20011107
			US 2001-331310P	P 20011114
			US 2001-341237P	P 20011220
			US 2002-369860P	P 20020405
			US 2002-139785	A2 20020507
			US 2002-403382P	P 20020815
			US 2002-425730P	P 20021113
			US 2003-468050P	P 20030506
			WO 2003-US25457	A2 20030815
			US 2004-608362P	P 20040910
			US 2004-986047	A2 20041112
			US 2004-986349	B2 20041112
			US 2005-666161P	P 20050330
			US 2006-391384	A2 20060329
			US 2007-885979P	P 20070122
			US 2007-990697P	P 20071128
			AU 2002-309647	A3 20020507
			JP 2003-500202	A3 20020507

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

#### ABSTRACT:

The present invention relates to antibodies and related mols. that immunospecifically bind to TRAIL receptor, TR4. Such antibodies have uses, for example, in the prevention and treatment of cancers and other proliferative disorders. The invention also relates to nucleic acid mols. encoding anti-TR4 antibodies, vectors and host cells containing these nucleic acids, and methods for

producing the same. The present invention relates to methods and compns. for preventing, detecting, diagnosing, treating or ameliorating a disease or disorder, especially cancer and other hyperproliferative disorders, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related mols., that immunospecifically bind to TRAIL receptor TR4.

IT **437742-34-2P**, NPI-0052

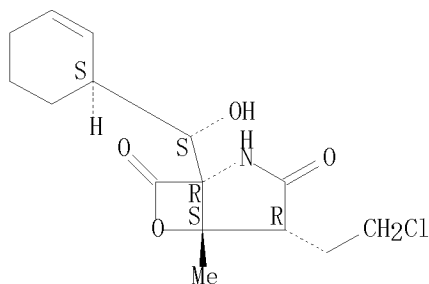
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(anti-human TRAIL receptor TR4 antibodies and scFvs for diagnosis and treatment of cancer or hyperproliferative disease)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 3

THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD  
(3 CITINGS)

L6 ANSWER 48 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2009:1014125 CAPLUS

DOCUMENT NUMBER: 151:243398

TITLE: PSMB10 (proteasome beta 10 subunit) expression as diagnosis marker and drug target of chronic rejection, proteasome inhibitors for treating chronic rejection

INVENTOR(S): Brouard, Sophie; Giral, Magali; Soulillou, Jean-Paul; Jovanovic, Vojislav; Ashton-Chess, Joanna

PATENT ASSIGNEE(S): Institut National de la Sante et de la Recherche Medicale (INSERM, Fr.; TC Land Expression

SOURCE: PCT Int. Appl., 43pp.; Chemical Indexing Equivalent to 151:243397 (EP)

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009101083	A1	20090820	WO 2009-EP51511	20090210
<p>W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW</p> <p>RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM</p>				
EP 2088205	A1	20090812	EP 2008-300084	20080211
<p>R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS</p>				
CA 2715050	A1	20090820	CA 2009-2715050	20090210
EP 2245183	A1	20101103	EP 2009-711003	20090210
<p>R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS</p>				
PRIORITY APPLN. INFO. :		EP 2008-300084		A 20080211
		WO 2009-EP51511		W 20090210

## ABSTRACT:

The present invention relates to a method of diagnosing chronic graft rejection of a grafted organ in a subject using PSMB10 (proteasome beta 10), an interferon inducible catalytic subunit of the immunoproteasome. The inventors identified PSMB10 as being upregulated in situations of chronic rejection, both in rat models and in human patients. The upregulation of PSMB10 was confirmed both in blood and in biopsies. The invention provides a method for diagnosing chronic graft rejection comprising: (a) determining in vitro an expression level value for PSMB10 in said subject biol. sample, (b) comparing said value to at least one reference expression level value for PSMB10 in at least one reference sample, and (c) diagnosing if said subject is or not undergoing chronic rejection of said grafted organ. The invention also concerns a diagnostic kit or microarray for performing the method of the invention. The invention further concerns the medical use of proteasome inhibitors for treating chronic rejection.

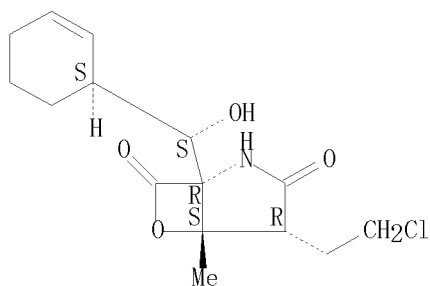
IT 437742-34-2

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (proteasome inhibitor; PSMB10 (proteasome beta 10 subunit) expression as diagnosis marker and drug target of chronic rejection, proteasome inhibitors for treating chronic rejection)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



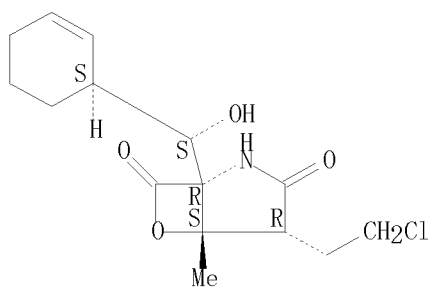
IT 437742-34-2D, analogs

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (proteasome inhibitors; PSMB10 (proteasome beta 10 subunit) expression  
 as diagnosis marker and drug target of chronic rejection, proteasome  
 inhibitors for treating chronic rejection)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT:

4

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 49 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:989338 CAPLUS  
 DOCUMENT NUMBER: 151:350327  
 TITLE: Snapshots of the Fluorosalinoporamide/20S Complex  
 Offer Mechanistic Insights for Fine Tuning Proteasome  
 Inhibition  
 AUTHOR(S): Groll, Michael; McArthur, Katherine A.; Macherla,  
 Venkat R.; Manam, Rama Rao; Potts, Barbara C.  
 CORPORATE SOURCE: Center for Integrated Protein Science at the  
 Department of Chemistry, Lehrstuhl für Biochemie,  
 Technische Universität München, Garching, D-85747,  
 Germany  
 SOURCE: Journal of Medicinal Chemistry (2009), 52(17),  
 5420-5428  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 ABSTRACT:

Many marketed drugs contain fluorine, reflecting its ability to modulate a variety of biol. responses. The unique 20S proteasome inhibition profile of fluorosalinosporamide compared to chlorinated anticancer agent salinosporamide A (NPI-0052) is exemplary and relates to each halogen's leaving group potential. Crystal structures of fluoro-, hydroxy-, and bromosalinosporamide in complex with the yeast 20S proteasome core particle (CP) provide mechanistic insights into ligand binding and leaving group elimination and the ability to fine-tune the duration of proteasome inhibition. Fluorosalinoporamide/CP crystal structures determined over time offer striking snapshots of the ligand trapped with an intact fluoroethyl group in anticipation of fluoride elimination, followed by complete nucleophilic displacement of fluoride to give the highly stabilized cyclic ether found for salinosporamide A and bromosalinosporamide. This two-step reaction pathway is consistent with a mechanism for partially reversible proteasome inhibition by fluorosalinosporamide. Proteasome catalyzed fluoride displacement provides preliminary insights into the active site Thr1N pKa.

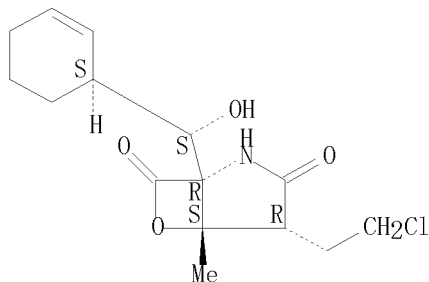
IT 437742-34-2, Salinosporamide A 889457-14-1

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (crystal structure and snapshots of fluorosalinosporamide/20S complex offer mechanistic insights for fine tuning proteasome inhibition)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

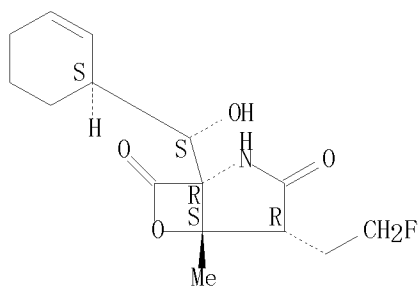


RN 889457-14-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-fluoroethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.





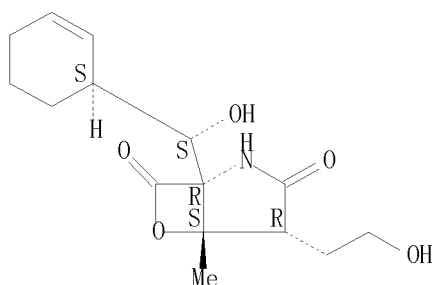
IT 823229-54-5 863126-95-8 872360-15-1

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(crystal structure and snapshots of fluorosalinosporamide/20S complex offer mechanistic insights for fine tuning proteasome inhibition)

RN 823229-54-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

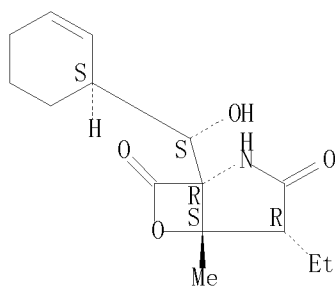
Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

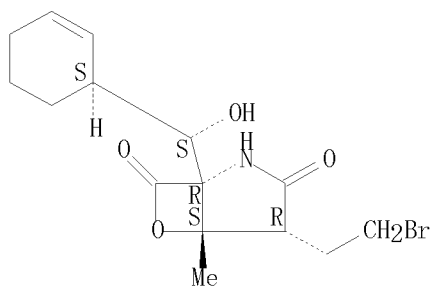
Absolute stereochemistry. Rotation (-).



RN 872360-15-1 CAPLUS

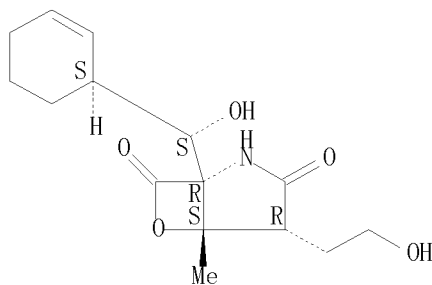
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



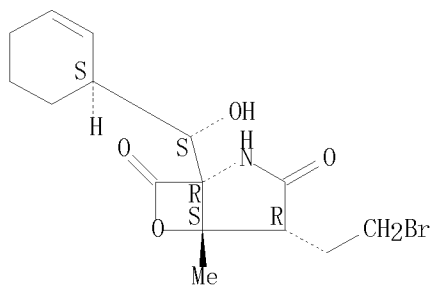
IT 823229-54-5DP, complex with 20S proteasome  
872360-15-1DP, complex with 20S proteasome 889457-14-1DP  
 , complex with 20S proteasome  
 RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)  
 (crystal structure; crystal structure and snapshots of  
 fluorosalinoporamide/20S complex offer mechanistic insights for fine  
 tuning proteasome inhibition)  
 RN 823229-54-5 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



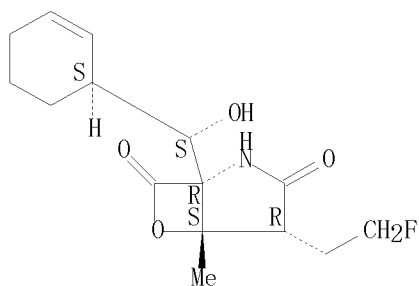
RN 872360-15-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 889457-14-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-fluoroethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD  
(7 CITINGS)  
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 50 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2009:975021 CAPLUS

DOCUMENT NUMBER: 151:353907

TITLE: Biosynthesis of the salinosporamide A polyketide synthase substrate chloroethylmalonyl-coenzyme A from S-adenosyl-L-methionine

AUTHOR(S): Eusthuio, Alessandra S.; McGlinchey, Ryan P.; Liu, Yuan; Hazzard, Christopher; Beer, Laura L.; Florova, Galina; Alhamadsheh, Mamoun M.; Lechner, Anna; Kale, Andrew J.; Kobayashi, Yoshihisa; Reynolds, Kevin A.; Moore, Bradley S.

CORPORATE SOURCE: Scripps Institution of Oceanography, University of California at San Diego, La Jolla, CA, 92093-0204, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2009), 106(30), 12295-12300, S12295/1-S12295/12

CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 151:353907

ABSTRACT:

Polyketides are among the major classes of bioactive natural products used to treat microbial infections, cancer, and other diseases. Here we describe a pathway to chloroethylmalonyl-CoA as a polyketide synthase building block in the biosynthesis of salinosporamide A, a marine microbial metabolite whose chlorine atom is crucial for potent proteasome inhibition and anticancer activity. S-adenosyl-L-methionine (SAM) is converted to 5'-chloro-5'-deoxyadenosine (5'-CIDA) in a reaction catalyzed by a SAM-dependent chlorinase as previously reported. By using a combination of gene deletions, biochem. analyses, and chemical complementation expts. with putative intermediates, we now provide evidence that 5'-CIDA is converted to chloroethylmalonyl-CoA in a 7-step route via the penultimate intermediate 4-chlorocrotonyl-CoA. Because halogenation often increases the bioactivity of drugs, the availability of a halogenated polyketide building block may be useful in mol. engineering approaches toward polyketide scaffolds.

IT 437742-34-2P, Salinosporamide A 863126-95-8P,

Salinosporamide B

RL: BMF (Bioindustrial manufacture); BSU (Biological study, unclassified);

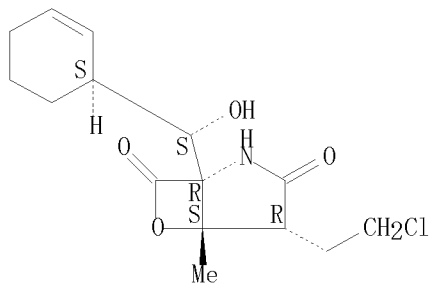
BIOL (Biological study); PREP (Preparation)

(biosynthesis of salinosporamide polyketide synthase substrate chloroethylmalonyl-CoA from S-adenosyl-L-methionine)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

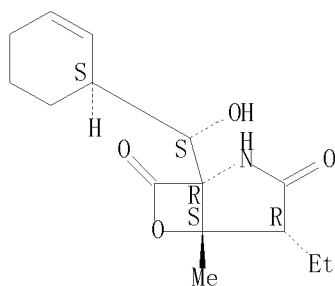
Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	2	THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT:	29	THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 51 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:971129 CAPLUS  
 DOCUMENT NUMBER: 151:243397  
 TITLE: PSMB10 (proteasome beta 10 subunit) expression as  
 diagnosis marker and drug target of chronic rejection,  
 proteasome inhibitors for treating chronic rejection  
 INVENTOR(S): Brouard, Sophie; Giral, Magali; Soulillou, Jean-Paul;  
 Jovanovic, Vojislav; Ashton-Chess, Joanna  
 PATENT ASSIGNEE(S): Institut National de la Sante et de la Recherche  
 Medicale (INSERM, Fr.  
 SOURCE: Eur. Pat. Appl., 24pp.; Chemical Indexing Equivalent  
 to 151:243398 (WO)  
 CODEN: EPXXDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 2088205	A1	20090812	EP 2008-300084	20080211
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS				
CA 2715050	A1	20090820	CA 2009-2715050	20090210
WO 2009101083	A1	20090820	WO 2009-EP51511	20090210
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
EP 2245183	A1	20101103	EP 2009-711003	20090210
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS				
PRIORITY APPLN. INFO. :			EP 2008-300084	A 20080211
			WO 2009-EP51511	W 20090210

## ABSTRACT:

The present invention relates to a method of diagnosing chronic graft rejection of a grafted organ in a subject using PSMB10 (proteasome beta 10), an interferon inducible catalytic subunit of the immunoproteasome. The inventors identified PSMB10 as being upregulated in situations of chronic rejection, both in rat models and in human patients. The upregulation of PSMB10 was confirmed both in blood and in biopsies. The invention provides a method for diagnosing chronic graft rejection comprising: (a) determining in vitro an expression level value for PSMB10 in said subject biol. sample, (b) comparing said value to at least one reference expression level value for PSMB10 in at least one reference sample, and (c) diagnosing if said subject is or not undergoing chronic rejection of said grafted organ. The invention also concerns a diagnostic kit or microarray for performing the method of the invention. The invention further concerns the medical use of proteasome inhibitors for treating chronic rejection.

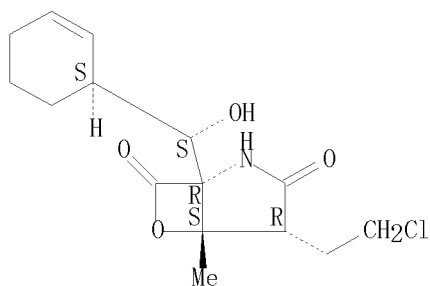
IT **437742-34-2**, Salinosporamide A

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (proteasome inhibitor; PSMB10 (proteasome beta 10 subunit) expression as diagnosis marker and drug target of chronic rejection, proteasome inhibitors for treating chronic rejection)

RN 437742-34-2 CAPLUS

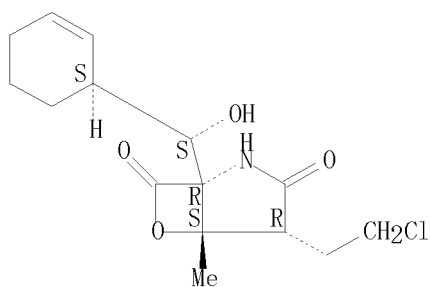
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 437742-34-2D, Salinosporamide A, analogs  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (proteasome inhibitors; PSMB10 (proteasome beta 10 subunit) expression  
 as diagnosis marker and drug target of chronic rejection, proteasome  
 inhibitors for treating chronic rejection)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 52 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2009:898642 CAPLUS

DOCUMENT NUMBER: 151:373283

TITLE: Inhibition of epithelial to mesenchymal transition in metastatic prostate cancer cells by the novel proteasome inhibitor, NPI-0052: Pivotal roles of Snail repression and RKIP induction

AUTHOR(S): Baritaki, S.; Chapman, A.; Yeung, K.; Spandidos, D. A.; Palladino, M.; Bonavida, B.

CORPORATE SOURCE: Department of Microbiology, Immunology and Molecular Genetics, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, Los Angeles, CA, USA

SOURCE: Oncogene (2009), 28(40), 3573-3585

CODEN: ONCNES; ISSN: 0950-9232

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Metastasis is associated with the loss of epithelial features and the acquisition of mesenchymal characteristics and invasive properties by tumor cells, a process known as epithelial to mesenchymal transition (EMT). Snail expression, through nuclear factor (NF)- $\kappa$ B activation, is an EMT determinant. The proteasome inhibitor, NPI-0052, induces the metastasis tumor suppressor/immune surveillance cancer gene, Raf kinase inhibitor protein (RKIP), via NF- $\kappa$ B inhibition. We hypothesized that NPI-0052 may inhibit Snail expression and, consequently, the metastatic phenotype in DU-145 prostate cancer cells. Cell treatment with NPI-0052 induced E-cadherin and inhibited Snail expression and both tumor cell invasion and migration. Inhibition of Snail inversely correlated with the induction of RKIP. The underlying mechanism of NPI-0052-induced inhibition of the metastatic phenotype was corroborated by: (1) treatment with Snail siRNA in DU-145 inhibited EMT and, in contrast, overexpression of Snail in the nonmetastatic LNCaP cells induced EMT, (2) NPI-0052-induced repression of Snail via inhibition of NF- $\kappa$ B was corroborated by the specific NF- $\kappa$ B inhibitor DHMEQ and (3) RKIP overexpression mimicked NPI-0052 in the inhibition of Snail and EMT. These findings demonstrate, for the first time, the role of NPI-0052 in the regulation of EMT via inhibition of NF- $\kappa$ B and Snail and induction of RKIP.

IT **437742-34-2**, NPI-0052

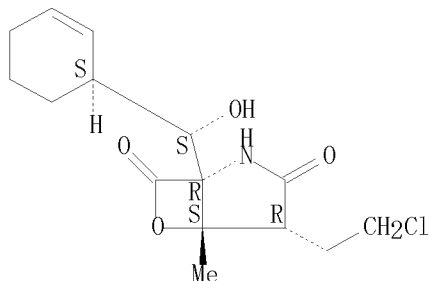
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(inhibition of epithelial to mesenchymal transition in metastatic prostate cancer cells by novel proteasome inhibitor NPI-0052 pivotal roles of Snail repression and RKIP induction)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 53 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:897434 CAPLUS  
DOCUMENT NUMBER: 151:542702  
TITLE: Piling up the JNK. Drug synergy through ER stress  
AUTHOR(S): Hertan, Lauren M.; Koumenis, Constantinos  
CORPORATE SOURCE: Department of Radiation Oncology, University of  
Pennsylvania, Philadelphia, PA, USA  
SOURCE: Cancer Biology & Therapy (2009), 8(9), 820-822  
CODEN: CBTAAO; ISSN: 1538-4047  
PUBLISHER: Landes Bioscience  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

A review. The research of Dasmahapatra et al. (2009) entitled BCL-2 antagonists interact synergistically with bortezomib in DLBCL cells in association with JNK activation and induction of ER stress is reviewed with commentary and refs. Dasmahapatra et al. provide intriguing data suggesting yet another possible mode of interaction of these two classes of inhibitors, which is centered on the activation of the stress kinase JNK and induction of ER stress by bortezomib. During ER stress, the unfolded protein response is activated as a mechanism for maintaining homeostasis between protein load and folding capacity in the ER. However, with excessive or prolonged activation, the UPR can also have a cytotoxic effect. It has been proposed that this may be caused by JNK-phosphorylation and inactivation of the anti-apoptotic regulator Bcl-2.

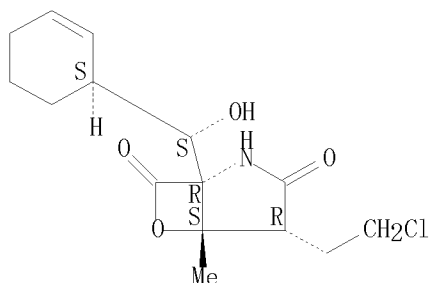
IT **437742-34-2**, NPI-0052

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(role of JNK and increased endoplasmic reticulum stress in cell death)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



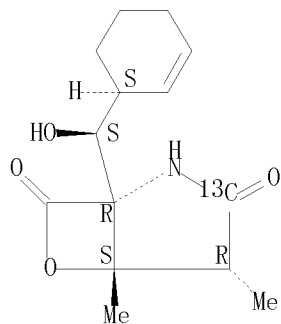
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 54 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:847356 CAPLUS  
DOCUMENT NUMBER: 151:239858  
TITLE: Biosynthesis of Salinosporamides from  
 $\alpha,\beta$ -Unsaturated Fatty Acids: Implications  
for Extending Polyketide Synthase Diversity  
AUTHOR(S): Liu, Yuan; Hazzard, Christopher; Eustaquio, Alessandra  
S.; Reynolds, Kevin A.; Moore, Bradley S.  
CORPORATE SOURCE: Scripps Institution of Oceanography and the Skaggs  
School of Pharmacy and Pharmaceutical Sciences,  
University of California at San Diego, La Jolla, CA,  
92093-0204, USA  
SOURCE: Journal of the American Chemical Society (2009),  
131(30), 10376-10377  
CODEN: JACSAT; ISSN: 0002-7863  
PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
OTHER SOURCE(S): CASREACT 151:239858  
ABSTRACT:

A new series of CoA-tethered polyketide synthase extender units were discovered in relation to the biosynthesis of the salinosporamide family of anticancer agents from the marine bacterium *Salinispora tropica*. In vivo and in vitro expts. revealed that the crotonyl-CoA reductase/carboxylase SalG has broad substrate tolerance toward 2-alkenyl-CoAs that give rise to the salinosporamide C-2 substitution pattern.

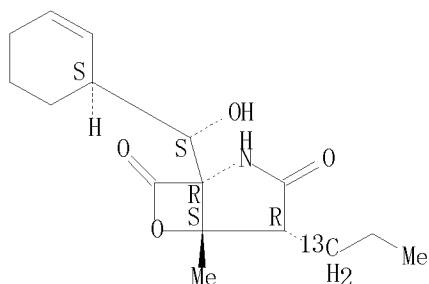
IT 1176732-52-7P 1176732-55-0P  
RL: BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)  
(biosynthesis of salinosporamides D and E from methylmalonyl-CoA and propylmalonyl-CoA in *Salinispora tropica* in relation to polyketide synthase diversity)  
RN 1176732-52-7 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4R,5S)-  
(CA INDEX NAME)

Absolute stereochemistry.



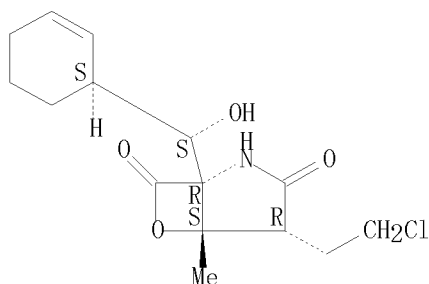
RN 1176732-55-0 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-(propyl-1-13C)-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



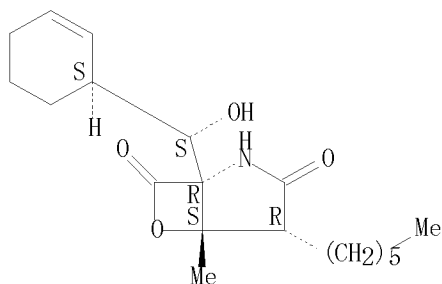
IT 437742-34-2, Salinosporamide A 744200-66-6,  
 Cinnabaramide A 823229-26-1, Salinosporamide D  
863126-95-8, Salinosporamide B 872360-15-1,  
 Bromosalinosporamide 872360-24-2, Salinosporamide E  
889457-14-1, Fluorosalinosporamide  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (biosynthesis of salinosporamides D and E from methylmalonyl-CoA and  
 propylmalonyl-CoA in *Salinispora tropica* in relation to polyketide  
 synthase diversity)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



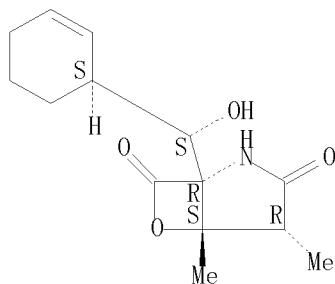
RN 744200-66-6 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-, (1R, 4R, 5S)-  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



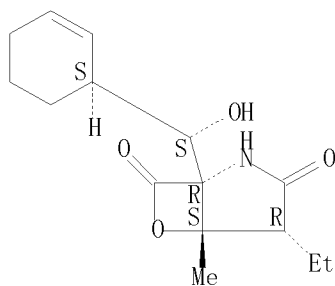
RN 823229-26-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R, 4R, 5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



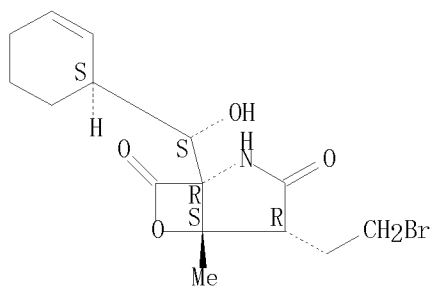
RN 863126-95-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



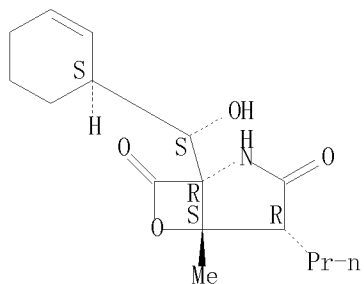
RN 872360-15-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



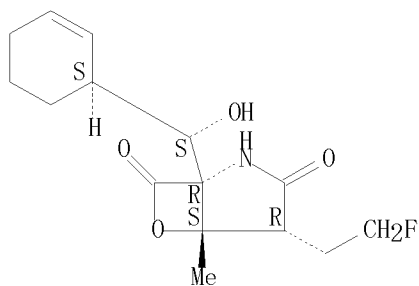
RN 872360-24-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



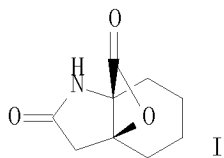
RN 889457-14-1 CAPLUS  
 CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-fluoroethyl)-5-methyl-,  
 (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT:	16	THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)
REFERENCE COUNT:	27	THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 55 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:814708 CAPLUS  
 DOCUMENT NUMBER: 151:313257  
 TITLE: Propellane as a conformational device for the  
 stabilization of the  $\beta$ -lactone of salinosporamide  
 A  
 AUTHOR(S): Vamos, Mitchell; Kobayashi, Yoshihisa  
 CORPORATE SOURCE: Department of Chemistry and Biochemistry, University  
 of California, San Diego, La Jolla, CA, 92093-0343,  
 USA  
 SOURCE: Tetrahedron (2009), 65(31), 5899-5903  
 CODEN: TETRAB; ISSN: 0040-4020  
 PUBLISHER: Elsevier Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 151:313257  
 GRAPHIC IMAGE:

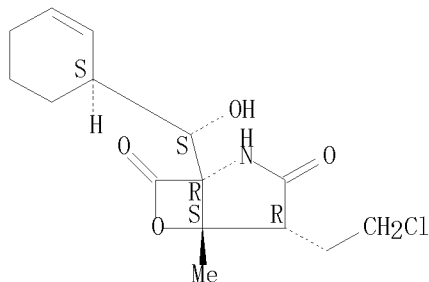


# ABSTRACT:

The synthesis of a propellane derivative I of salinosporamide A having increased stability under physiol.-like conditions was reported. The synthesis took advantage of a substrate-controlled stereoselective Ugi 4-center 3-component reaction to construct the required syn-bicyclic pyroglutamic acid framework.

IT 437742-34-2DP, Salinosporamide A, analogs  
 RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)  
 (propellane as a conformational device for the stabilization of the  
 $\beta$ -lactone of salinosporamide A)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
 (1 CITINGS)  
 REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 56 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2009:787638 CAPLUS

DOCUMENT NUMBER: 152:95253

TITLE: Beyond monoclonal antibodies: new therapeutic agents in non-Hodgkin's lymphomas

AUTHOR(S): Delmonte, Angelo; Ghielmini, Michele; Sessa, Cristiana

CORPORATE SOURCE: Oncology Institute of Southern Switzerland, Ospedale S. Giovanni, Bellinzona, Switz.

SOURCE: Oncologist (2009), 14(5), 511-525

CODEN: OCOLF6; ISSN: 1083-7159

PUBLISHER: AlphaMed Press

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ABSTRACT:

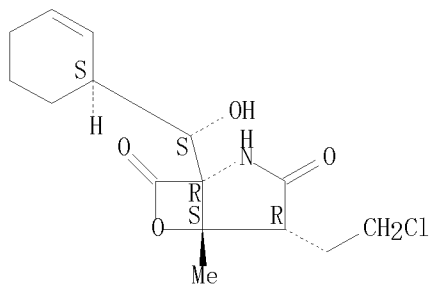
A review. The availability of active monoclonal antibodies, either as single agents or in combination with cytotoxic agents, has improved treatment results in non-Hodgkin's lymphoma (NHL). Despite this and the increasing number of available active monoclonal antibodies, alone or conjugated with radioisotopes, not all types of lymphoma are sensitive to these biol. agents and often they become resistant because of different mol. mechanisms. New mol. targets in neoplastic cells are emerging and provide the rationale for novel discovery initiatives. In fact, a greater knowledge of the biol. of lymphoma and the identification of compds. selectively active against a potential therapeutic pathway have already improved the time to progression and survival time of patients with some subtypes of NHL. The growing list of new drugs provides the exciting prospect of developing disease-specific and even patient-specific therapies. The aim of this review is to identify and discuss non-monoclonal antibody new therapeutic agents in terms of mechanism of action and clin. results. The preclin. and clin. features of proteasome inhibitors, histone deacetylase inhibitors, thalidomide and lenalidomide, mammalian target of rapamycin inhibitors, antisense oligonucleotides, heat shock protein inhibitors, protein kinase C inhibitors, antiangiogenic agents, and new cytotoxics are reviewed.

IT **437742-34-2**, Salinosporamide ARL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(new therapeutic agents in non-Hodgkin's lymphoma)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 133 THERE ARE 133 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L6 ANSWER 57 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:739404 CAPLUS  
 DOCUMENT NUMBER: 151:70266  
 TITLE: Methods of using [3.2.0] heterocyclic compounds and  
 analogs thereof in treating Waldenstrom's  
 macroglobulinemia  
 INVENTOR(S): Ghobrial, Irene; Roccaro, Aldo; Chauhan, Dharminder;  
 Anderson, Kenneth; Palladino, Michael A.  
 PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA; Dana-Farber Cancer  
 Institute  
 SOURCE: U.S. Pat. Appl. Publ., 62pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20090156469	A1	20090618	US 2008-329504	20081205
PRIORITY APPLN. INFO.:			US 2007-12396P	P 20071207
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT				
OTHER SOURCE(S): MARPAT 151:70266				

## ABSTRACT:

Disclosed are methods of treating Waldenstrom's Macroglobulinemia comprising administering to the animal, a therapeutically effective amount of a heterocyclic compound disclosed here.

IT 1044999-00-9P

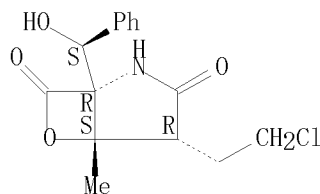
RL: PAC (Pharmacological activity); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(73heterocyclic compds. and analogs for treating Waldenstrom's macroglobulinemia)

RN 1044999-00-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

IT 437742-34-2P 863126-95-8P 872360-15-1P

RL: NPO (Natural product occurrence); PAC (Pharmacological activity); PUR (Purification or recovery); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

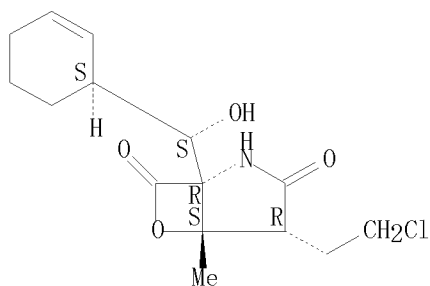
(heterocyclic compds. and analogs for treating Waldenstrom's macroglobulinemia)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

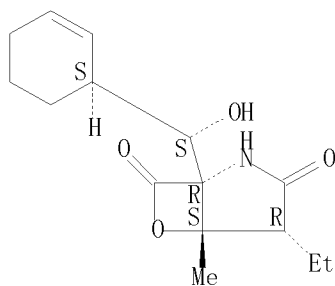




RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

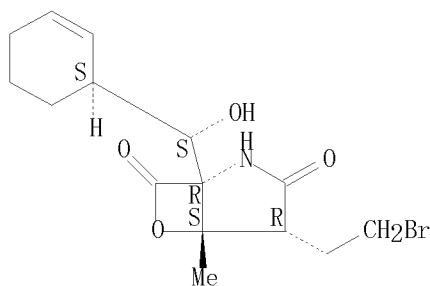
Absolute stereochemistry. Rotation (-).



RN 872360-15-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 1057246-20-4P      1057246-23-7P      1057246-24-8P  
1078724-63-6P      1161845-80-2P      1161845-81-3P

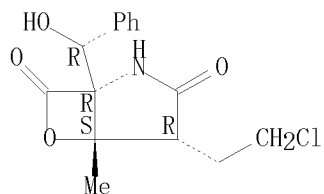
RL: PAC (Pharmacological activity); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(heterocyclic compds. and analogs for treating Waldenstrom's macroglobulinemia)

RN 1057246-20-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

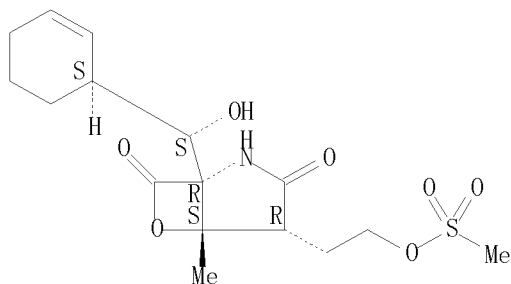
Absolute stereochemistry.



RN 1057246-23-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-  
[(methylsulfonyl)oxy]ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

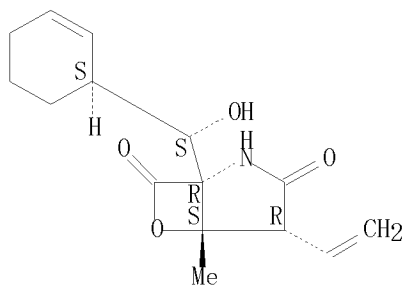
Absolute stereochemistry.



RN 1057246-24-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethenyl-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

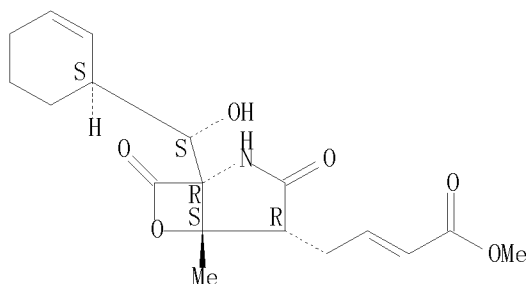
Absolute stereochemistry.



RN 1078724-63-6 CAPLUS

CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.  
Double bond geometry unknown.



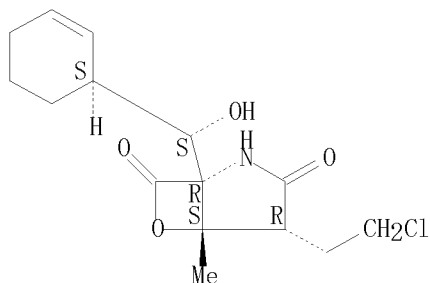
RN 1161845-80-2 CAPLUS

CN INDEX NAME NOT YET ASSIGNED

CM 1

CRN 437742-34-2  
 CMF C15 H20 Cl N O4

Absolute stereochemistry. Rotation (-).

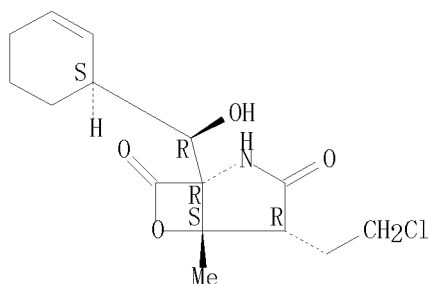


RN 1161845-81-3 CAPLUS  
 CN INDEX NAME NOT YET ASSIGNED

CM 1

CRN 872360-18-4  
 CMF C15 H20 Cl N O4

Absolute stereochemistry.



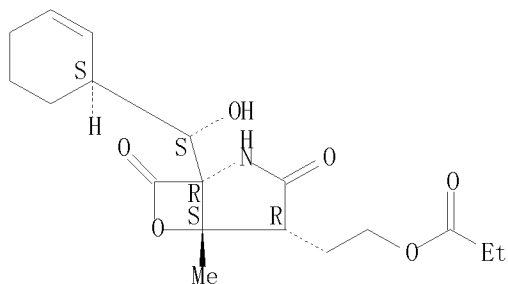
IT 823229-56-7P 872360-18-4P 872360-22-0P  
872360-23-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (heterocyclic compds. and analogs for treating Waldenstrom's macroglobulinemia)

RN 823229-56-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

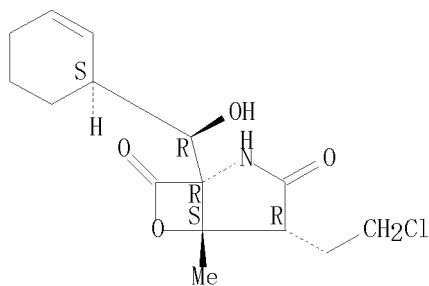


RN 872360-18-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,

4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

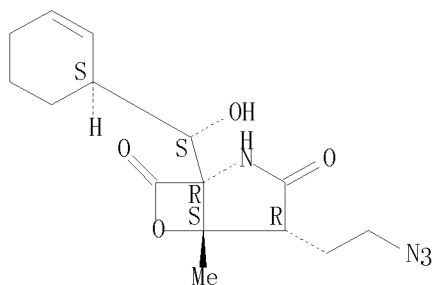
Absolute stereochemistry.



RN 872360-22-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-azidoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

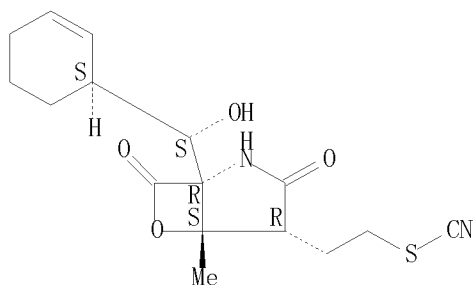
Absolute stereochemistry.



RN 872360-23-1 CAPLUS

CN Thiocyanic acid, 2-[(1R,4R,5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA INDEX NAME)

Absolute stereochemistry.



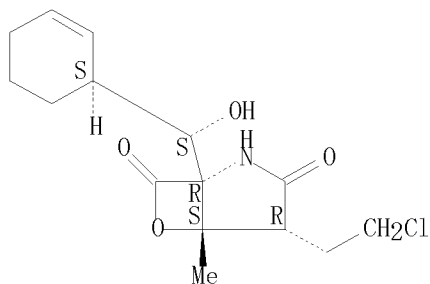
IT 437742-34-2D, derivs. 823229-34-1D, derivs.  
863126-95-8D, derivs. 872360-15-1D, derivs.  
889457-14-1 889457-14-1D, derivs.

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(heterocyclic compds. and analogs for treating Waldenstrom's  
macroglobulinemia)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

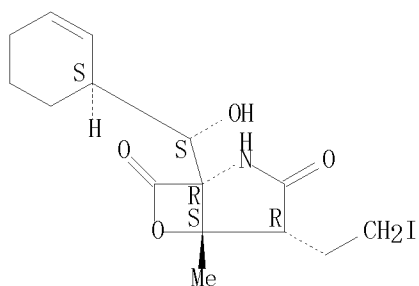
Absolute stereochemistry. Rotation (-).



RN 823229-34-1 CAPLUS

CN 6-0xa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

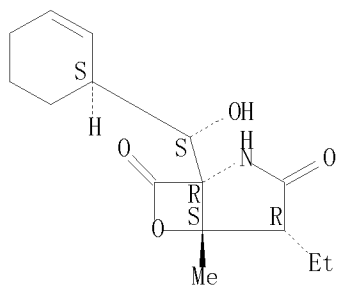
Absolute stereochemistry.



RN 863126-95-8 CAPLUS

CN 6-0xa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R, 4R, 5S)-  
(CA INDEX NAME)

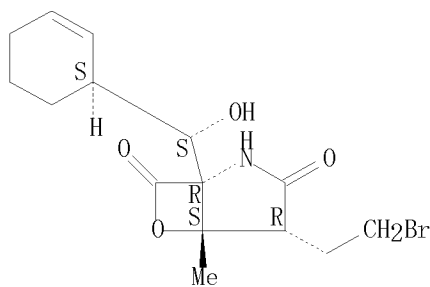
Absolute stereochemistry. Rotation (-).



RN 872360-15-1 CAPLUS

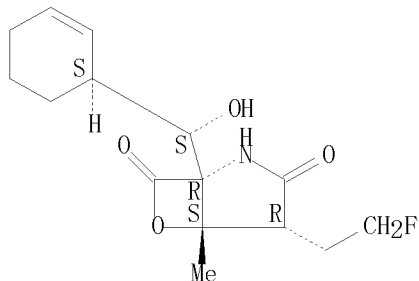
CN 6-0xa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



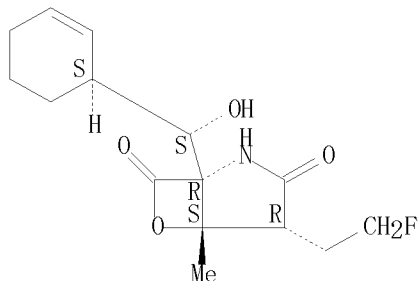
RN 889457-14-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-fluoroethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



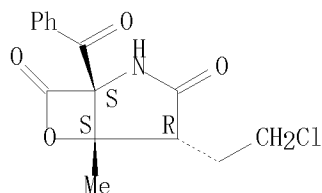
RN 889457-14-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-fluoroethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



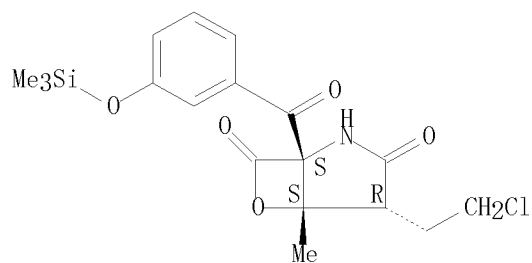
IT 1057246-19-1P 1057385-27-9P 1067236-86-5P  
1070997-86-2P 1161845-78-8P  
 RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP  
 (Preparation); RACT (Reactant or reagent)  
 (heterocyclic compds. and analogs for treating Waldenström's  
 macroglobulinemia)  
 RN 1057246-19-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-benzoyl-4-(2-chloroethyl)-5-methyl-, (1S,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



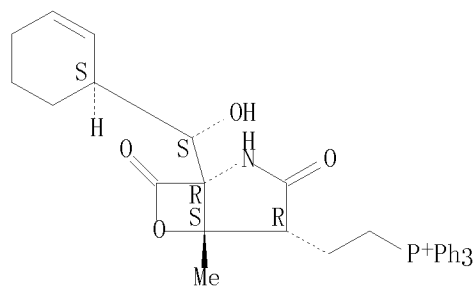
RN 1057385-27-9 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-5-methyl-1-[3-[(trimethylsilyl)oxy]benzoyl]-,  
 (1S,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1067236-86-5 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

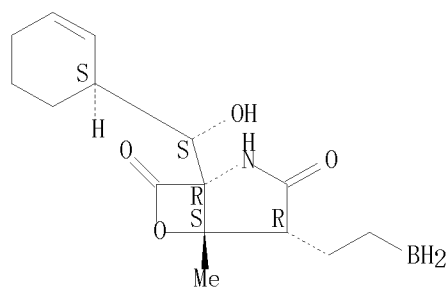
Absolute stereochemistry.



● I<sup>-</sup>

RN 1070997-86-2 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

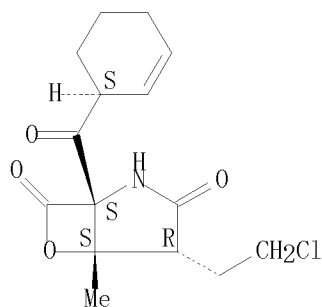


RN 1161845-78-8 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

CM 1

CRN 872360-17-3  
CMF C15 H18 Cl N O4

Absolute stereochemistry.



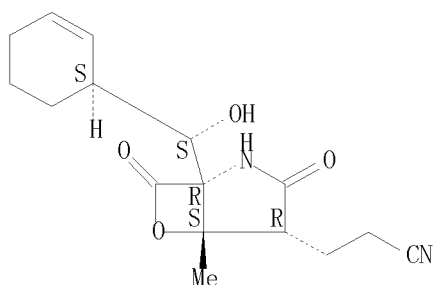
IT **1057246-22-6P**

RL: PRPH (Prophetic); SPN (Synthetic preparation); PREP (Preparation)  
(heterocyclic compds. and analogs for treating Waldenstrom's  
macroglobulinemia)

RN 1057246-22-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-4-propanenitrile,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-,  
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT **823229-34-1P**

**823229-54-5P**

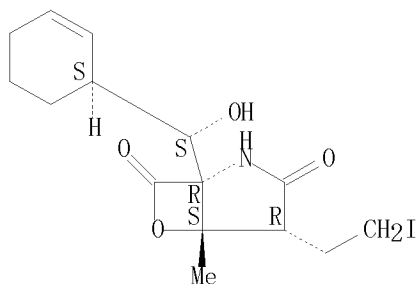
**872360-17-3P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(heterocyclic compds. and analogs for treating Waldenstrom's  
macroglobulinemia)

RN 823229-34-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.

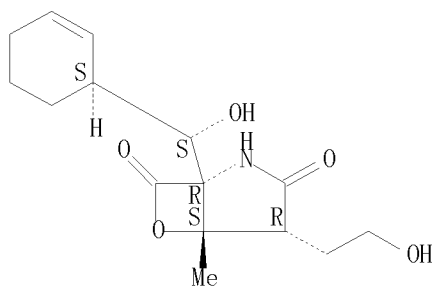


RN 823229-54-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

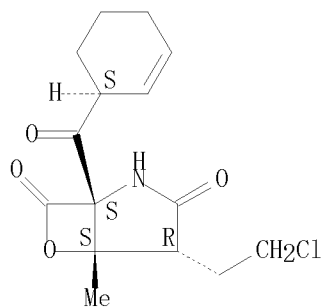




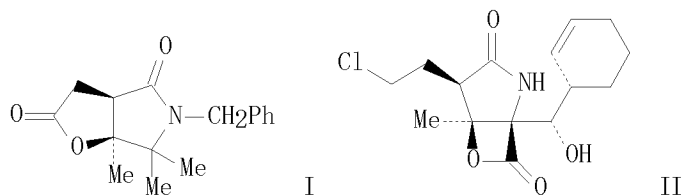
RN 872360-17-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
(1S, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 58 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:663494 CAPLUS  
 DOCUMENT NUMBER: 151:198109  
 TITLE: Formal synthesis of salinosporamide A via  
 NHC-catalyzed intramolecular lactonization  
 AUTHOR(S): Struble, Justin R.; Bode, Jeffrey W.  
 CORPORATE SOURCE: Roy and Diana Vagelos Laboratories, Department of  
 Chemistry, University of Pennsylvania, Philadelphia,  
 PA, 19104-6354, USA  
 SOURCE: Tetrahedron (2009), 65(26), 4957-4967  
 CODEN: TETRAB; ISSN: 0040-4020  
 PUBLISHER: Elsevier Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 151:198109  
 GRAPHIC IMAGE:



# ABSTRACT:

An N-heterocyclic carbene (NHC) catalyzed intramol. lactonization to prepare densely functionalized bicyclic  $\gamma$ -lactam- $\gamma$ -lactone adducts, e.g. I, from enals, e.g. (E)-MeCOC(Me)2N(CH2Ph)COCH:CHCHO, is reported. This method has been applied to the formal synthesis of salinosporamide A (II), a potent 20S proteasome inhibitor and anti-cancer therapeutic.

IT **437742-34-2P**, Salinosporamide A

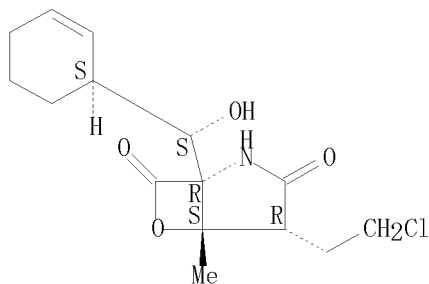
RL: SPN (Synthetic preparation); PREP (Preparation)

(N-heterocyclic carbene-catalyzed intramol. lactonization to prepare bicyclic  $\gamma$ -lactam- $\gamma$ -lactone adducts and application to formal synthesis of salinosporamide A)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS  
 RECORD (11 CITINGS)  
 REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 59 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:649756 CAPLUS  
DOCUMENT NUMBER: 151:1309  
TITLE: Treatment of histone deacetylase mediated disorders  
INVENTOR(S): Gore, Lia; De Ryckere, Deborah  
PATENT ASSIGNEE(S): University of Colorado, USA  
SOURCE: PCT Int. Appl., 73pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

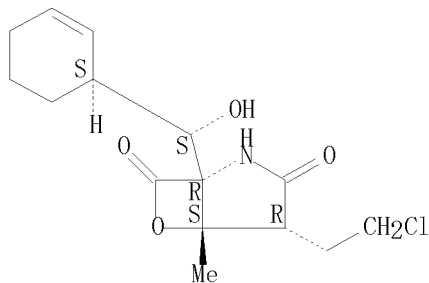
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009067543	A2	20090528	WO 2008-US84072	20081119
WO 2009067543	A3	20090903		
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
US 20110053991	A1	20110303	US 2010-743809	20101111
PRIORITY APPLN. INFO. :			US 2007-989053P	P 20071119
			WO 2008-US84072	W 20081119

## ABSTRACT:

Provided herein are pharmaceutical agents, pharmaceutical compns., methods of treatment, treatment regimens and kits for the treatment of histone deacetylase (HDAC) mediated disorders, such as cancer. Methods include administering to a patient a first amount of a Class I selective HDAC inhibitor and a second amount of a second HDAC inhibitor.

IT **437742-34-2**, Salinosporamide A  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(treatment of histone deacetylase mediated disorders such as cancer  
with Class inhibitor and second inhibitor and combination with other  
agents)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 60 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:615928 CAPLUS  
DOCUMENT NUMBER: 150:555811  
TITLE: Combinations of HDAC inhibitors and proteasome  
inhibitors  
INVENTOR(S): Gore, Lia; Deryckere, Deborah  
PATENT ASSIGNEE(S): University of Colorado, USA  
SOURCE: U.S. Pat. Appl. Publ., 30pp.  
CODEN: USXXCO  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20090131367	A1	20090521	US 2008-273350	20081118
WO 2009067453	A1	20090528	WO 2008-US83926	20081118
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			

PRIORITY APPLN. INFO.: US 2007-989063P P 20071119

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

ABSTRACT:

Provided herein are pharmaceutical agents, pharmaceutical compns., methods of treatment, treatment regimens and kits for the treatment of cancer.

IT **437742-34-2**, NPI-0052

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

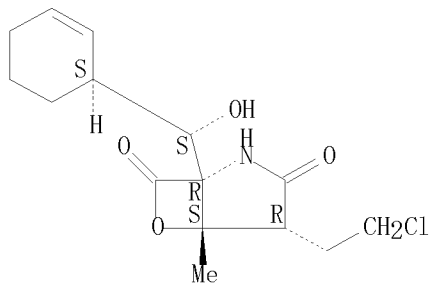
(Biological study); USES (Uses)

(salinosporamide A; combinations of HDAC inhibitors and proteasome inhibitors)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
(1 CITINGS)

L6 ANSWER 61 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2009:585134 CAPLUS

DOCUMENT NUMBER: 151:211692

TITLE: Caspase-8 dependent histone acetylation by a novel proteasome inhibitor, NPI-0052: a mechanism for synergy in leukemia cells

AUTHOR(S): Miller, Claudia P.; Rudra, Sharmistha; Keating, Michael J.; Wierda, William G.; Palladino, Michael; Chandra, Joya

CORPORATE SOURCE: Department of Pediatrics Research, University of Texas M. D. Anderson Cancer Center, Houston, USA

SOURCE: Blood (2009), 113(18), 4289-4299

CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: American Society of Hematology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Combination studies of histone deacetylase inhibitors (HDACi) and proteasome inhibitors are providing preclin. framework to build better strategies against hematol. malignancies. Our previous work found that a novel proteasome inhibitor, NPI-0052, and HDACi synergistically induce apoptosis in leukemia cells in a caspase-8- and oxidant-dependent manner. Here we extend those observations to primary leukemia cells and identify novel mechanisms of synergy. Because the proximal targets of NPI-0052 and HDACi are inhibition of proteasome activity and histone acetylation, we initially examined those biochem. events. Increased acetylation of histone-H3 was detected in Jurkat and CLL primary cells treated with NPI-0052, alone or in combination with various HDACi (MS/SNDX-275 or vorinostat). Hyperacetylation by NPI-0052 occurred to a lesser extent in caspase-8-deficient cells and in cells treated with an antioxidant. These results indicate that NPI-0052 is eliciting caspase-8 and oxidative stress-dependent epigenetic alterations. In addition, real-time PCR revealed that MS/SNDX-275 repressed expression of the proteasomal  $\beta 5$ ,  $\beta 2$ , and  $\beta 1$  subunits, consequently inhibiting resp. enzymic activities. Overall, our results suggest that crosstalk by NPI-0052 and HDACi are contributing, along with caspase-8 activation and oxidative stress, to their synergistic cytotoxic effects in leukemia cells, reinforcing the potential clin. utility of combining these 2 agents.

IT 437742-34-2, NPI-0052

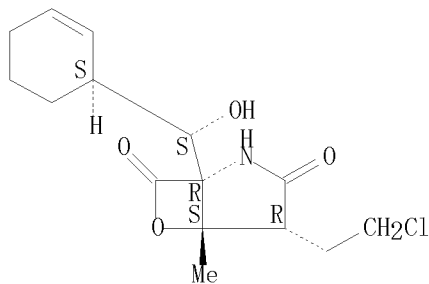
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(synergistic mechanisms between proteasome and histone deacetylase inhibitors)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 62 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:523337 CAPLUS  
 DOCUMENT NUMBER: 150:492919  
 TITLE: Combination therapy of a type II anti-CD20 antibody  
 with a proteasome inhibitor  
 INVENTOR(S): Fertig, Georg; Friess, Thomas; Klein, Christian;  
 Umana, Pablo  
 PATENT ASSIGNEE(S): F. Hoffmann-La Roche AG, Switz.; GlycArt Biotechnology  
 AG  
 SOURCE: PCT Int. Appl., 42 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009053038	A2	20090430	WO 2008-EP8919	20081022
WO 2009053038	A3	20090625		
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
US 20090110688	A1	20090430	US 2008-234759	20080922
AU 2008315926	A1	20090430	AU 2008-315926	20081022
KR 2010068292	A	20100622	KR 2010-7009027	20081022
AR 71733	A1	20100714	AR 2008-104606	20081022
EP 2205318	A2	20100714	EP 2008-841724	20081022
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS			
JP 2011500741	T	20110106	JP 2010-530330	20081022
MX 2010004164	A	20100804	MX 2010-4164	20100416
IN 2010CN02251	A	20101015	IN 2010-CN2251	20100420
PRIORITY APPLN. INFO.:			EP 2007-20820	A 20071024
			WO 2008-EP8919	W 20081022

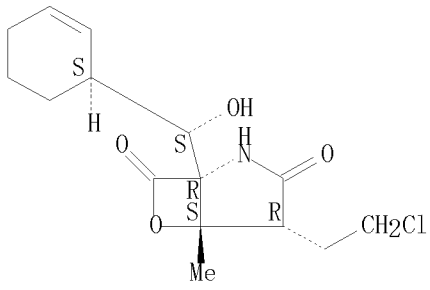
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

#### ABSTRACT:

The present invention is directed to the use an type II anti-CD20 antibody for the manufacture of a medicament for the treatment of cancer, especially of CD20 expressing cancers in combination with a proteasome inhibitor.

IT **437742-34-2**, Salinosporamide a  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combination therapy of a type II anti-CD20 antibody with a proteasome inhibitor)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD  
(2 CITINGS)

L6 ANSWER 63 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2009:520533 CAPLUS

DOCUMENT NUMBER: 151:96777

TITLE: Effect of cobalt and vitamin B12 on the production of salinosporamides by *Salinispora tropica*

AUTHOR(S): Tsueng, Ginger; Sing Lam, Kin

CORPORATE SOURCE: Nereus Pharmaceuticals Inc., San Diego, CA, USA

SOURCE: Journal of Antibiotics (2009), 62(4), 213-216

CODEN: JANTAJ; ISSN: 0021-8820

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

In this study, we provide data on the effect of cobalt on the production of NPI-0047 and the two closely related salinosporamides, NPI-0052 and NPI-2065 by *Salinispora tropica*. As cobalt is an essential component of vitamin B12, a coenzyme involved in methylation and carbon skeletal rearrangement reactions, we also examined the effect of vitamin B12 on the production of salinosporamides.

IT 437742-34-2, NPI 0052 863126-95-8, NPI 0047

872360-11-7, NPI 2065

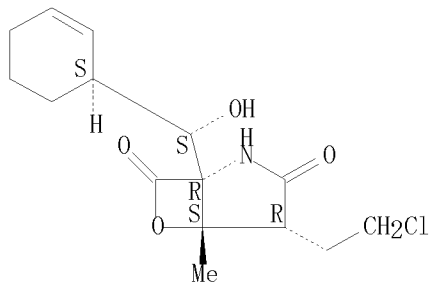
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(effect of cobalt and vitamin B12 on production of salinosporamides by *Salinispora tropica*)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

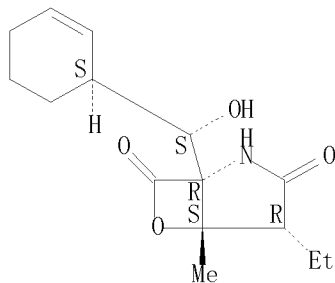
Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

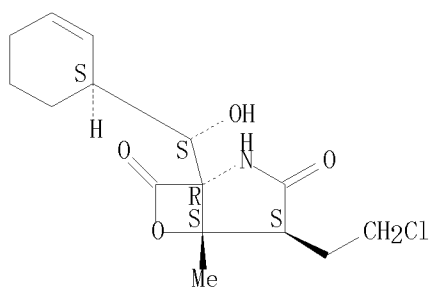


RN 872360-11-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.





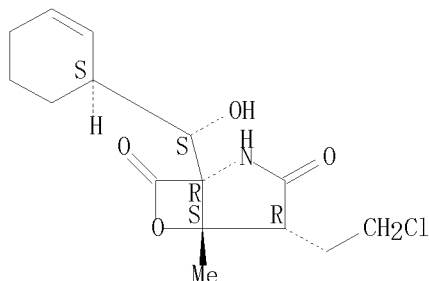
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD  
(2 CITINGS)  
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 64 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:482612 CAPLUS  
DOCUMENT NUMBER: 151:542593  
TITLE: Antitumor compounds from actinomycetes: from gene clusters to new derivatives by combinatorial biosynthesis  
AUTHOR(S): Olano, Carlos; Mendez, Carmen; Salas, Jose A.  
CORPORATE SOURCE: Departamento de Biologia Funcional and Instituto Universitario de Oncologia del Principado de Asturias (I.U.O.P.A.), Universidad de Oviedo, Oviedo, 33006, Spain  
SOURCE: Natural Product Reports (2009), 26(5), 628-660  
CODEN: NPRRDF; ISSN: 0265-0568  
PUBLISHER: Royal Society of Chemistry  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

A review. Antitumor compds. produced by actinomycetes and novel derivs. generated by combinatorial biosynthesis are reviewed (with 318 refs. cited). The different structural groups for which the relevant gene clusters were isolated and characterized are reviewed, with a description of the strategies used for the generation of the novel derivs. and the activities of these compds. against tumor cell lines.

IT **437742-34-2**, Salinosporamide A  
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(antitumor compds. from actinomycetes)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)  
REFERENCE COUNT: 318 THERE ARE 318 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 65 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:351958 CAPLUS  
DOCUMENT NUMBER: 150:530119  
TITLE: Discovery and development of the anticancer agent  
salinosporamide A (NPI-0052)  
AUTHOR(S): Fenical, William; Jensen, Paul R.; Palladino, Michael  
A.; Lam, Kin S.; Lloyd, G. Kenneth; Potts, Barbara C.  
CORPORATE SOURCE: Center for Marine Biotechnology and Biomedicine,  
Scripps Institution of Oceanography, University of  
California, San Diego, La Jolla, CA, 92093-0204, USA  
SOURCE: Bioorganic & Medicinal Chemistry (2009), 17(6),  
2175-2180  
CODEN: BMECEP; ISSN: 0968-0896  
PUBLISHER: Elsevier B.V.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

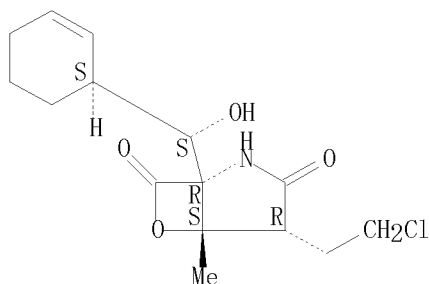
A review. The discovery of the anticancer agent salinosporamide A (NPI-0052) resulted from the exploration of new marine environments and a commitment to the potential of the ocean to yield new natural products for drug discovery and development. Driving the success of this process was the linkage of academic research together with the ability and commitment of industry to undertake drug development and provide the resources and expertise to advance the entry of salinosporamide A (NPI-0052) into human clin. trials. This paper offers a chronicle of the important events that facilitated the rapid clin. development of this exciting mol.

IT **437742-34-2**, Salinosporamide A  
RL: NPO (Natural product occurrence); THU (Therapeutic use); BIOL  
(Biological study); OCCU (Occurrence); USES (Uses)  
(discovery and development of anticancer agent salinosporamide A  
(NPI-0052))

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

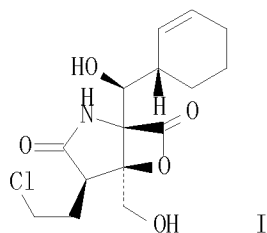
Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 33 THERE ARE 33 CAPLUS RECORDS THAT CITE THIS  
RECORD (33 CITINGS)  
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 66 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:268956 CAPLUS  
 DOCUMENT NUMBER: 150:306373  
 TITLE: Preparation of cyclic-fused  $\beta$ -lactones as prodrugs  
 INVENTOR(S): Romo, Daniel; Henry-Riyad, Huda; Lee, Changsuk; Nguyen, Henry; Oh, Seongho; Purohit, Vikram C.  
 PATENT ASSIGNEE(S): The Texas A&M University System, USA  
 SOURCE: U.S. Pat. Appl. Publ., 58 pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20090062547	A1	20090305	US 2007-775216	20070709
PRIORITY APPLN. INFO.:			US 2006-819444P	P 20060707
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT				
OTHER SOURCE(S): CASREACT 150:306373; MARPAT 150:306373				
GRAPHIC IMAGE:				



#### ABSTRACT:

The present invention provides a concise synthetic method for generating lactam-fused  $\beta$ -lactones, e.g. I, that feature, in some embodiments, a tertiary fused carbinol, quaternary carbons, and a reactive beta-lactone moiety available for further reactions. The present invention further provides compds. synthesized by this method as well as methods of using these compds. as inhibitors of the proteasome and fatty acid synthase.

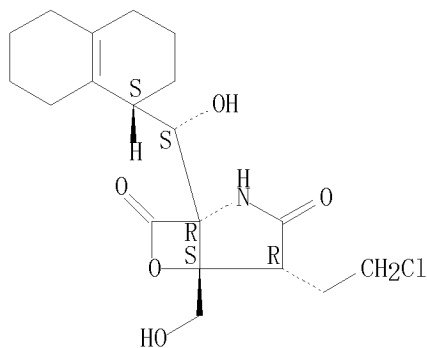
#### IT 1127249-49-3P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of cyclic-fused  $\beta$ -lactones as prodrugs and as inhibitors of proteasome 20S)

RN 1127249-49-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-5-(hydroxymethyl)-1-[(S)-hydroxy[(1S)-1,2,3,4,5,6,7,8-octahydro-1-naphthalenyl]methyl]-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 1127249-44-8P 1127249-45-9P 1127249-46-0P1127249-82-4P

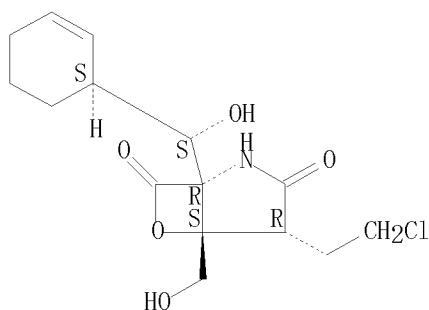
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of cyclic-fused  $\beta$ -lactones as prodrugs and as inhibitors of proteasome 20S)

RN 1127249-44-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-(hydroxymethyl)-, (1R,4R,5S)- (CA INDEX NAME)

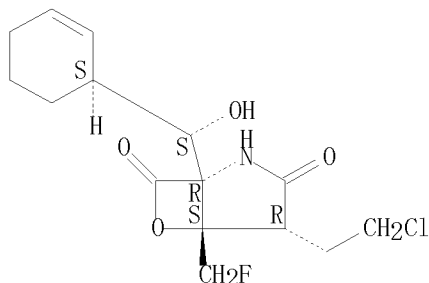
Absolute stereochemistry.



RN 1127249-45-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-(fluoromethyl)-, (1R,4R,5S)- (CA INDEX NAME)

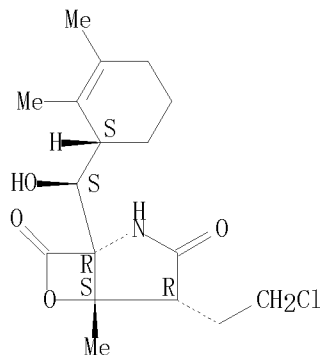
Absolute stereochemistry.



RN 1127249-46-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-[(1S)-2,3-dimethyl-2-cyclohexen-1-yl]hydroxymethyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

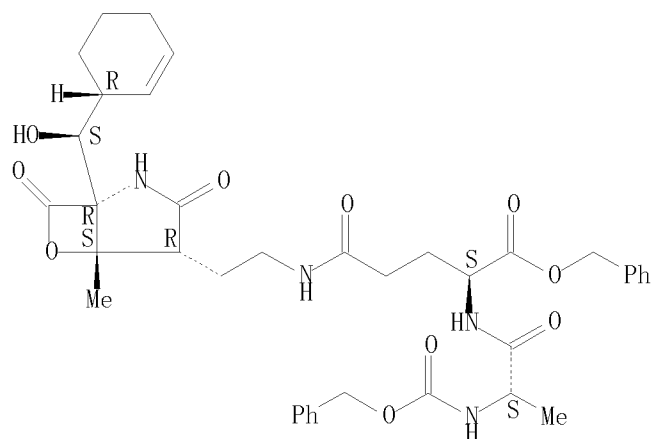


RN 1127249-82-4 CAPLUS

CN L-Glutamine, N-[(phenylmethoxy)carbonyl]-L-alanyl-N-[2-[(1R,4R,5S)-1-[(S)-

(1R)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl]-, phenylmethyl ester (CA INDEX NAME)

Absolute stereochemistry.



IT 437742-34-2P, (-)-Salinosporamide A 1127249-71-1P

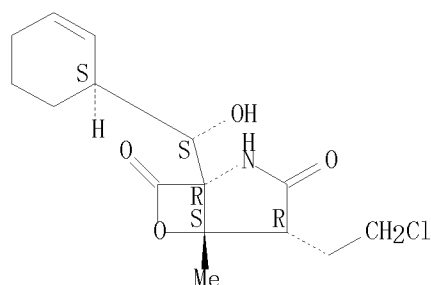
1127249-72-2P

RL: PRPH (Prophetic); SPN (Synthetic preparation); PREP (Preparation)  
(preparation of cyclic-fused  $\beta$ -lactones as prodrugs and as inhibitors  
of proteasome 20S)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

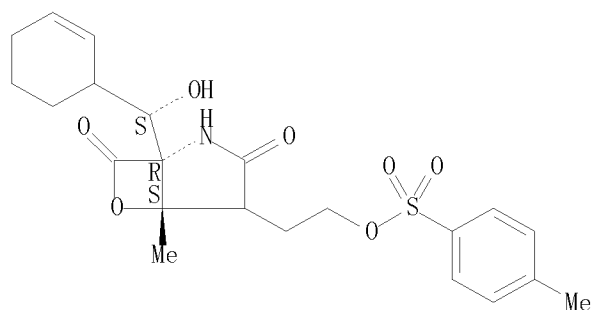
Absolute stereochemistry. Rotation (-).



RN 1127249-71-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-[(4-  
methylphenyl)sulfonyl]oxy]ethyl]-, (1R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

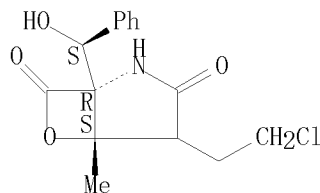


RN 1127249-72-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,

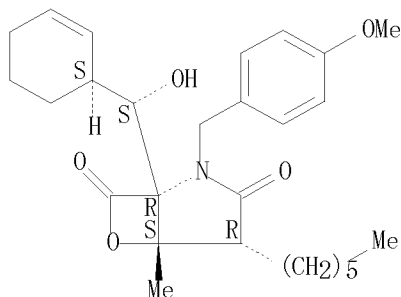
4-(2-chloroethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



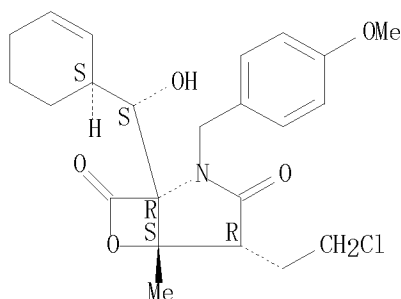
IT 942517-04-6P 942517-09-1P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of cyclic-fused  $\beta$ -lactones as prodrugs and as inhibitors of proteasome 20S)  
 RN 942517-04-6 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-2-[(4-methoxyphenyl)methyl]-5-methyl-, (1S,4S,5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



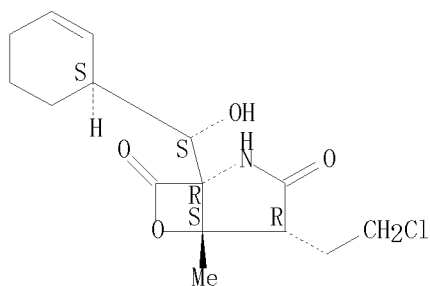
RN 942517-09-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-2-[(4-methoxyphenyl)methyl]-5-methyl-, (1S,4S,5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



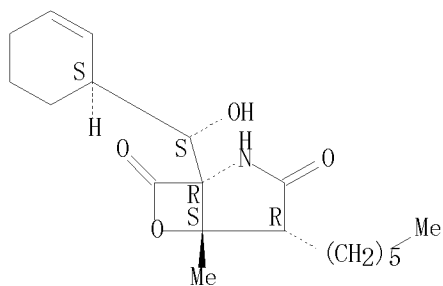
IT 909569-43-3P, ( $\pm$ )-SalinosporamideA 942516-89-4P,  
 ( $\pm$ )-CinnabaramideA 1127249-60-8P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of cyclic-fused  $\beta$ -lactones as prodrugs and as inhibitors of proteasome 20S)  
 RN 909569-43-3 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-, (1S,4S,5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



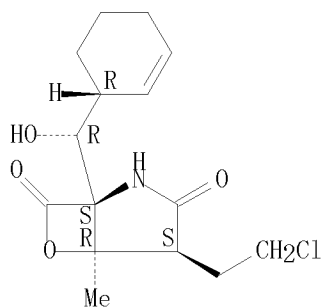
RN 942516-89-4 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-,  
 (1S, 4S, 5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



RN 1127249-60-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1S, 4S, 5R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



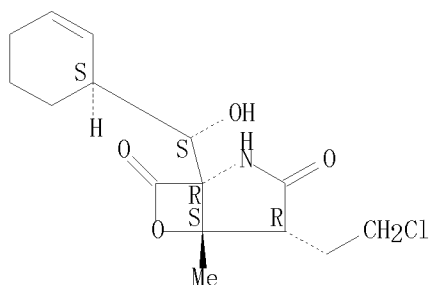


L6 ANSWER 67 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:255198 CAPLUS  
DOCUMENT NUMBER: 150:472933  
TITLE: Indium-catalyzed Conia-ene reaction for alkaloid synthesis  
AUTHOR(S): Hatakeyama, Susumi  
CORPORATE SOURCE: Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, 852-8521, Japan  
SOURCE: Pure and Applied Chemistry (2009), 81(2), 217-226  
CODEN: PACHAS; ISSN: 0033-4545  
PUBLISHER: International Union of Pure and Applied Chemistry  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

A review with refs. on indium-catalyzed Conia-ene reaction for alkaloid synthesis. In(OTf)<sub>3</sub>-catalyzed cyclization of nitrogen- and oxygen-tethered acetylenic malonic esters provides various five- to seven-membered heterocycles in moderate to excellent yield, and the reaction proceeds with no racemization and complete E-selectivity in the case of chiral and nonterminal alkynes. The synthetic utility is demonstrated by the synthesis of (-)-salinosporamide A, a highly potent 20S proteasome inhibitor, and (+)-neooxazolomycin, a member of the oxazolomycin family of antibiotics.

IT **437742-34-2P**, (-)-Salinosporamide A  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(indium-catalyzed Conia-ene reaction for alkaloid synthesis)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)  
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 68 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:250856 CAPLUS  
DOCUMENT NUMBER: 150:321368  
TITLE: Control of HIF-1 $\alpha$  Expression by eIF2 $\alpha$   
Phosphorylation-Mediated Translational Repression  
AUTHOR(S): Zhu, Keyi; Chan, WaiKin; Heymach, John; Wilkinson,  
Miles; McConkey, David J.  
CORPORATE SOURCE: Departments of Cancer Biology, Urology, The University  
of Texas M. D. Anderson Cancer Center, Houston, TX,  
77030, USA  
SOURCE: Cancer Research (2009), 69(5), 1836-1843  
CODEN: CNREA8; ISSN: 0008-5472  
PUBLISHER: American Association for Cancer Research  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
ABSTRACT:

Hypoxia inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) plays a central role in regulating tumor angiogenesis via its effects on vascular endothelial growth factor (VEGF) transcription, and its expression is regulated through proteasome-mediated degradation. Paradoxically, previous studies have shown that proteasome inhibitors (PI) block tumor angiogenesis by reducing VEGF expression, but the mechanisms have not been identified. Here, we report that PIs down-regulated HIF-1 $\alpha$  protein levels and blocked HIF-1 $\alpha$  transcriptional activity in human prostate cancer cells. PIs induced phosphorylation of the translation initiation factor 2 $\alpha$  (eIF2 $\alpha$ ), which caused general translational repression to inhibit HIF-1 $\alpha$  expression. Furthermore, PIs induced HIF-1 $\alpha$  accumulation in LNCaP-Pro5 cells depleted of eIF2 $\alpha$  via siRNA transfection and in MEFs expressing a phosphorylation-deficient mutant form of eIF2 $\alpha$ . Finally, PIs failed to induce eIF2 $\alpha$  phosphorylation or translational attenuation in DU145 or 253JB-V cells, and, in these cells, PIs promoted HIF-1 $\alpha$  accumulation. Our data established that PIs down-regulated HIF-1 $\alpha$  expression in cells that display activation of the unfolded protein response by stimulating phosphorylation of eIF2 $\alpha$  and inhibiting HIF-1 $\alpha$  translation.

IT **437742-34-2**, NPI-0052

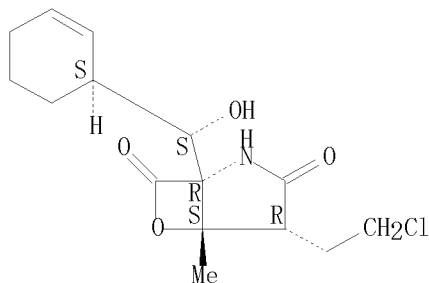
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(proteasome inhibitors down-regulate HIF-1 $\alpha$  expression in cancer cells that display activation of unfolded protein response by stimulating phosphorylation of eIF2 $\alpha$  and inhibiting HIF-1 $\alpha$  translation)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD  
(8 CITINGS)  
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 69 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:214409 CAPLUS  
 DOCUMENT NUMBER: 151:115307  
 TITLE: Finding NEMO (inhibitors) the search for marine  
 pharmacophores targeting the nuclear factor- $\kappa$ B  
 AUTHOR(S): Folmer, Florence; Schumacher, Marc; Diederich, Marc;  
 Jaspars, Marcel  
 CORPORATE SOURCE: European Centre for Marine Biotechnology, Aquapharm  
 Biodiscovery Ltd., Oban, Argyll, PA37 1QA, UK  
 SOURCE: Chimica Oggi (2008), 26(4), 40-42, 44-46  
 CODEN: CHOGDS; ISSN: 0392-839X  
 PUBLISHER: Tekno Scienze  
 DOCUMENT TYPE: Journal; General Review  
 LANGUAGE: English  
 ABSTRACT:

A review. Since the early 1960's, marine organisms have provided natural products chemists with a rich source of novel and very diverse metabolites with unprecedented chemical structures. Over the last few decades, significant effort has been placed on the pharmacol. evaluation of marine secondary metabolites. This scientific endeavour, which is often referred to as the search for "Drugs from the Sea", has lead to the discovery of numerous anti-cancer, anti-inflammatory, and antimicrobial compds., several of which are currently in clin. trials. In the present review, we discuss the potential of marine natural products as pharmacophores for the inhibition of the nuclear factor- $\kappa$ B which has recently been recognized as an important mol. target in both anti-cancer and anti-inflammatory drug discovery. In particular, we focus on marine natural products with lactone moieties, which cover a third of all the currently known NF- $\kappa$ B inhibitors of marine origin.

Abbreviations: COX-2, cyclooxygenase-2; I $\kappa$ B, inhibitor of NF- $\kappa$ B; JNK, Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; N.A., not available; NEMO, NF- $\kappa$ B essential modulator; IKK, kinase of I $\kappa$ B; iNOS, inducible nitric oxide synthase; IL, interleukin; NF- $\kappa$ B, nuclear factor- $\kappa$ B; PKC, protein kinase C; PLA2, phospholipase A2; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

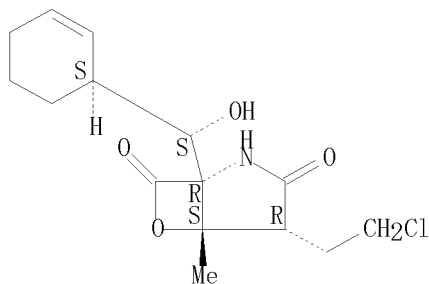
IT **437742-34-2**, Salinosporamide a

RL: NPO (Natural product occurrence); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)  
 (marine natural products including salinosporamide may be helpful as antiinflammatory, antimicrobial and anticancer agents)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
 (1 CITINGS)  
 REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 70 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:86451 CAPLUS  
 DOCUMENT NUMBER: 150:160095  
 TITLE: Use of adenosine A2A receptor agonists and  
 phosphodiesterase (PDE) inhibitors for the treatment  
 of B-cell proliferative disorders, and combinations  
 with other agents  
 INVENTOR(S): Rickles, Richard; Lee, Margaret S.  
 PATENT ASSIGNEE(S): CombinatoRx, Incorporated, USA  
 SOURCE: PCT Int. Appl., 70 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009011893	A2	20090122	WO 2008-US8758	20080717
WO 2009011893	A3	20090319		
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
AU 2008276451	A1	20090122	AU 2008-276451	20080717
CA 2694983	A1	20090122	CA 2008-2694983	20080717
US 20090053168	A1	20090226	US 2008-175219	20080717
EP 2178369	A2	20100428	EP 2008-780231	20080717
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS			
PRIORITY APPLN. INFO.:			US 2007-950307P	P 20070717
			US 2007-965587P	P 20070821
			WO 2008-US8758	W 20080717

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

#### ABSTRACT:

The invention provides compns. and methods for the treatment of B-cell proliferative disorders that employ an A2A receptor agonist or one or more PDE inhibitors. The methods and compns. may further include an antiproliferative compound

IT **437742-34-2**, NPI 0052

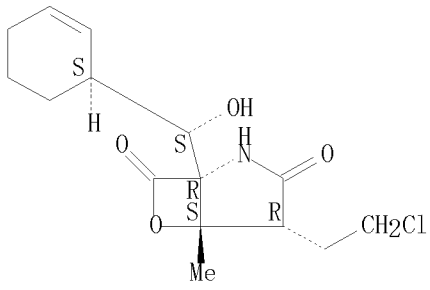
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(adenosine A2A receptor agonists and phosphodiesterase inhibitors for treatment of B-cell proliferative disorders, and combinations with other agents)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD  
(2 CITINGS)

L6 ANSWER 71 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:83374 CAPLUS  
 DOCUMENT NUMBER: 150:160094  
 TITLE: Combinations for the treatment of B-cell proliferative disorders  
 INVENTOR(S): Rickles, Richard; Pierce, Laura; Lee, Margaret S.  
 PATENT ASSIGNEE(S): Combinatorx, Incorporated, USA  
 SOURCE: PCT Int. Appl., 79pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009011897	A1	20090122	WO 2008-US8764	20080717
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2008276455	A1	20090122	AU 2008-276455	20080717
CA 2694987	A1	20090122	CA 2008-2694987	20080717
US 20090047243	A1	20090219	US 2008-175121	20080717
EP 2178370	A1	20100428	EP 2008-780237	20080717
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS				
PRIORITY APPLN. INFO. :			US 2007-959877P	P 20070717
			US 2007-965595P	P 20070821
			WO 2008-US8764	W 20080717

# ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

## ABSTRACT:

The invention features compns. and methods employing combinations of an A2A receptor agonist and a PDE (phosphodiesterase) inhibitor for the treatment of a B-cell proliferative disorder, e g, multiple myeloma. In at least one embodiment, the compns. of the invention comprise a PDE inhibitor active against at least two of PDE 2, 3,4, and 7. In at least one embodiment, the compns. of the invention comprises further administering an antiproliferative compound

IT **437742-34-2**, NPI 0052

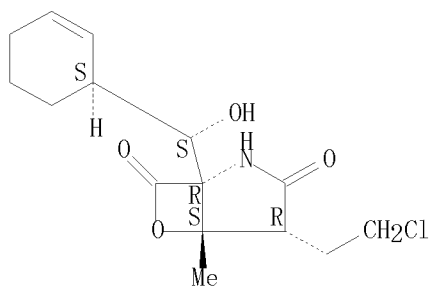
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combinations for treatment of B-cell proliferative disorders using PDE inhibitors and A2A receptor agonists and antiproliferative compds.)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
(1 CITINGS)  
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 72 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2009:77542 CAPLUS  
DOCUMENT NUMBER: 151:115147  
TITLE: Targeting the UPS as therapy in multiple myeloma  
AUTHOR(S): Chauhan, Dharminder; Bianchi, Giada; Anderson, Kenneth C.  
CORPORATE SOURCE: The Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115, USA  
SOURCE: BMC Biochemistry (2008), 9(Suppl. 1), No pp. given  
CODEN: BBMIB3  
URL: <http://www.biomedcentral.com/content/pdf/1471-2091-9-S1-S1.pdf>  
PUBLISHER: BioMed Central Ltd.  
DOCUMENT TYPE: Journal; General Review; (online computer file)  
LANGUAGE: English  
ABSTRACT:

A review. The coordinated regulation of cellular protein synthesis and degradation is essential for normal cellular functioning. The ubiquitin proteasome system mediates the intracellular protein degradation that is required for normal cellular homeostasis. The 26S proteasome is a multi-enzyme protease that degrades redundant proteins; conversely, inhibition of proteasomal degradation results in intracellular aggregation of unwanted proteins and cell death. This observation led to the development of proteasome inhibitors as therapeutics for use in cancer. The clin. applicability of targeting proteasomes is exemplified by the recent FDA approval of the first proteasome inhibitor, bortezomib, for the treatment of relapsed/refractory multiple myeloma. Although bortezomib represents a major advance in the treatment of this disease, it can be associated with toxicity and the development of drug resistance. Importantly, extensive preclin. studies suggest that combination therapies can both circumvent drug resistance and reduce toxicity. In addition, promising novel proteasome inhibitors, which are distinct from bortezomib, and exhibit equipotent anti-multiple myeloma activities, are undergoing clin. evaluation in order to improve patient outcome in multiple myeloma.

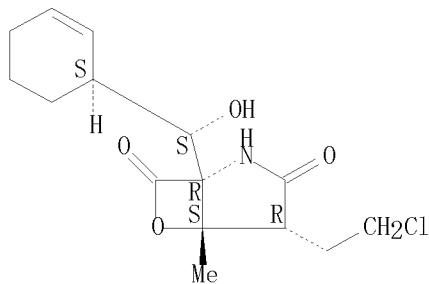
IT **437742-34-2**, NPI0052

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(novel NPI0052 distinct from bortezomib with equipotent anticancer activity and in combination with other drugs reduces drug resistance and toxicity in patient with refractory multiple myeloma)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

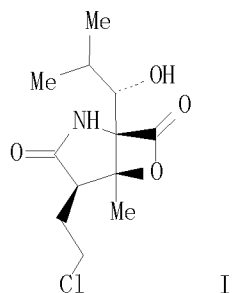
Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)  
REFERENCE COUNT: 110 THERE ARE 110 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 73 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2009:40709 CAPLUS  
 DOCUMENT NUMBER: 150:209033  
 TITLE: Antiprotealide is a natural product  
 AUTHOR(S): Manam, Rama Rao; Macherla, Venkat R.; Tsueng, Ginger;  
 Dring, Chris W.; Weiss, Jeffrey; Neuteboom, Saskia T.  
 C.; Lam, Kin S.; Potts, Barbara C.  
 CORPORATE SOURCE: Nereus Pharmaceuticals, Inc., San Diego, CA, 92121,  
 USA  
 SOURCE: Journal of Natural Products (2009), 72(2), 295-297  
 CODEN: JNPRDF; ISSN: 0163-3864  
 PUBLISHER: American Chemical Society-American Society of  
 Pharmacognosy  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GRAPHIC IMAGE:

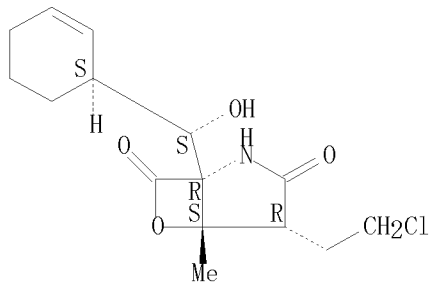


# ABSTRACT:

Large-scale fermentation of the marine actinomycete *Salinispora tropica* for production of salinosporamide A (NPI-0052; 1) clin. trials materials provided crude exts. containing minor secondary metabolites, including salinosporamide B (2) and a new congener (3). Spectroscopic characterization revealed that 3 is identical to antiprotealide (I), a mol. hybrid of 20S proteasome inhibitors 1 and omuralide (4) not previously described as a natural product. Anal. of crude exts. from shake flask cultures of three wild-type *S. tropica* strains confirmed the production of I at 1.1, 0.8, and 3.0 mg/L. Thus, I is a natural product metabolite of *S. tropica*.

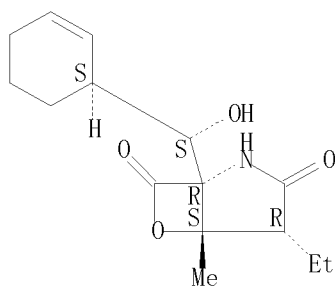
IT 437742-34-2P, Salinosporamide A 863126-95-8P,  
 Salinosporamide B  
 RL: BMF (Bioindustrial manufacture); BSU (Biological study, unclassified);  
 BIOL (Biological study); PREP (Preparation)  
 (antiprotealide is natural product from *Salinispora tropica*)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



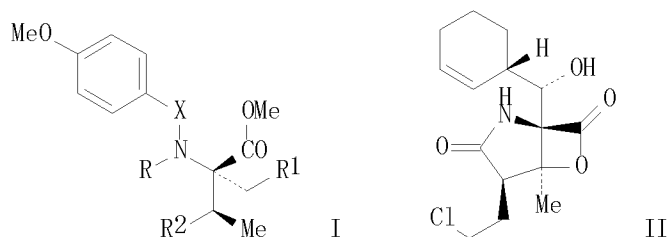
RN 863126-95-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	13	THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)
REFERENCE COUNT:	22	THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 74 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:1511250 CAPLUS  
 DOCUMENT NUMBER: 150:191183  
 TITLE: New synthetic route to access ( $\pm$ )-salinosporamideA  
 via an oxazolone-mediated ene-type reaction  
 AUTHOR(S): Mosey, Robert A.; Tepe, Jetze J.  
 CORPORATE SOURCE: Department of Chemistry, Michigan State University,  
 East Lansing, MI, 48824, USA  
 SOURCE: Tetrahedron Letters (2009), 50(3), 295-297  
 CODEN: TELEAY; ISSN: 0040-4039  
 PUBLISHER: Elsevier Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 150:191183  
 GRAPHIC IMAGE:



# ABSTRACT:

Synthesis of a racemic key intermediate I [R = COCH:CH<sub>2</sub>, R<sub>1</sub> = OCH<sub>2</sub>Ph, R<sub>2</sub> = oxo, X = CH<sub>2</sub>] for the synthesis of ( $\pm$ )-salinosporamideA (II) was reported. The synthesis of two precursors I [R = H, R<sub>1</sub> = OCH<sub>2</sub>Ph, R<sub>2</sub> = OH, X = CH<sub>2</sub>] and I [R = COCH:CH<sub>2</sub>, R<sub>1</sub> = OCH<sub>2</sub>Ph, R<sub>2</sub> = OH, X = CH<sub>2</sub>] of the target intermediate was achieved starting from ester I [R = COCH:CH<sub>2</sub>, R<sub>1</sub> = OCH<sub>2</sub>Ph, R<sub>2</sub> = OCMe<sub>3</sub>, X = CO] which had been prepared in previous work via an ene-type reaction of 4,5-dihydro-2-(4-methoxyphenyl)-5-oxo-4-oxazolecarboxylic acid Me ester with the enol ether H<sub>2</sub>C:CHOCHMe<sub>3</sub>.

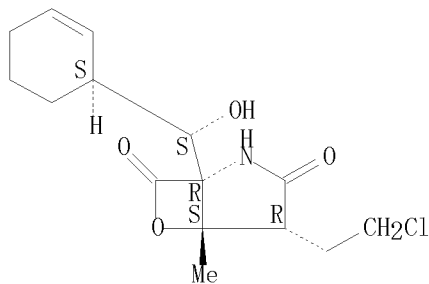
## IT 909569-43-3P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (synthetic route to ( $\pm$ )-salinosporamideA via an oxazolone-mediated ene-type reaction)

RN 909569-43-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1S,4S,5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS  
 RECORD (12 CITINGS)  
 REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 75 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:1369747 CAPLUS  
 DOCUMENT NUMBER: 149:548862  
 TITLE: Methods of using [3.2.0] heterocyclic compounds and  
 analogs thereof for treating infectious diseases  
 INVENTOR(S): Palladino, Michael  
 PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
 SOURCE: PCT Int. Appl., 133pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008137780	A2	20081113	WO 2008-US62553	20080502
WO 2008137780	A3	20090326		
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
US 20080280968	A1	20081113	US 2008-114449	20080502
US 20100168046	A1	20100701	US 2010-720557	20100309
PRIORITY APPLN. INFO.:			US 2007-916243P	P 20070504
			US 2008-114449	A1 20080502

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 149:548862

#### ABSTRACT:

Disclosed are methods of treating infectious diseases comprising administering to the animal, a therapeutically effective amount of a heterocyclic compound. The animal is a mammal, preferably a human or a rodent.

IT 437742-34-2P, Salinosporamide A

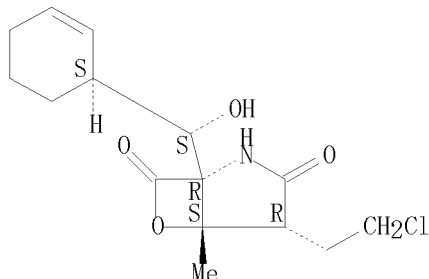
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); PUR (Purification or recovery); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(NPI-0052; heterocyclic compds. and analogs for treating infectious diseases)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 823229-34-1P 823229-56-7P 872360-18-4P  
872360-22-0P 872360-24-2P 1057246-22-6P  
1078636-12-0P

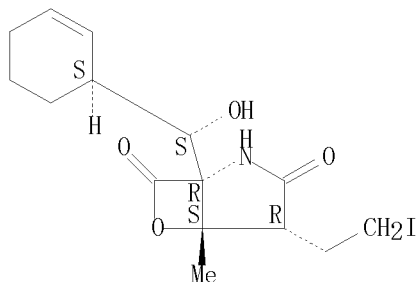
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(heterocyclic compds. and analogs for treating infectious diseases)

RN 823229-34-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

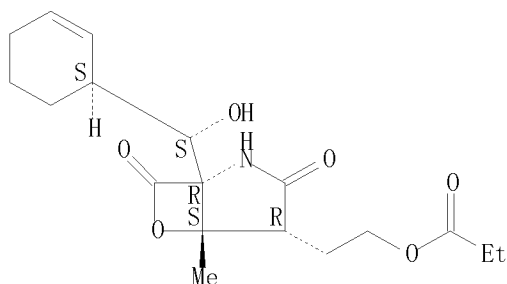
Absolute stereochemistry.



RN 823229-56-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

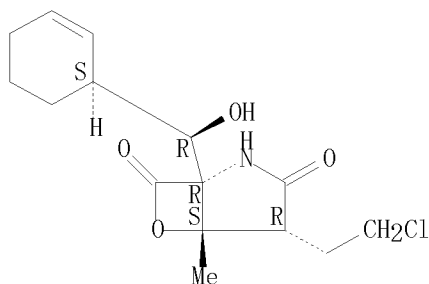
Absolute stereochemistry.



RN 872360-18-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

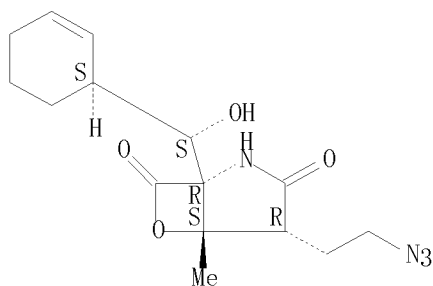
Absolute stereochemistry.



RN 872360-22-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-azidoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

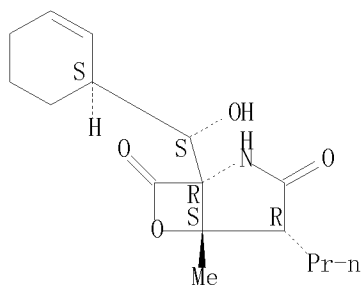
Absolute stereochemistry.



RN 872360-24-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-,  
(1R,4R,5S)- (CA INDEX NAME)

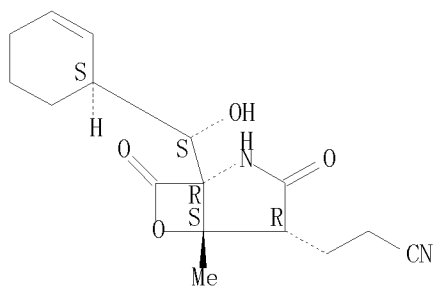
Absolute stereochemistry.



RN 1057246-22-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-4-propanenitrile,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-,  
(1R,4R,5S)- (CA INDEX NAME)

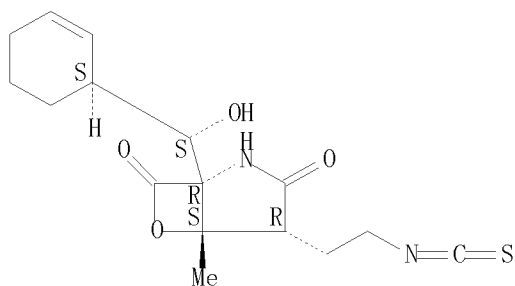
Absolute stereochemistry.



RN 1078636-12-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-isothiocyanatoethyl)-5-  
methyl-, (1R,4R,5S)- (CA INDEX NAME)

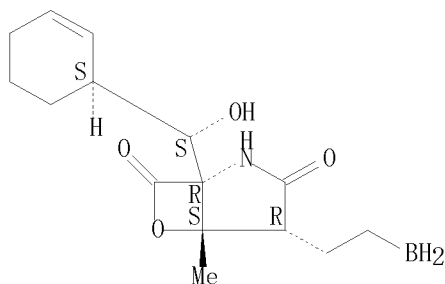
Absolute stereochemistry.

IT **1070997-86-2**RL: PRPH (Prophetic); RCT (Reactant); RACT (Reactant or reagent)  
(heterocyclic compds. and analogs for treating infectious diseases)

RN 1070997-86-2 CAPLUS

CN INDEX NAME NOT YET ASSIGNED

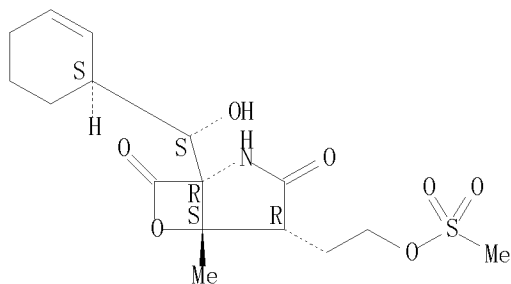
Absolute stereochemistry.

IT **1057246-23-7P** **1067236-86-5P**RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP  
(Preparation); RACT (Reactant or reagent)  
(heterocyclic compds. and analogs for treating infectious diseases)

RN 1057246-23-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-  
[(methylsulfonyl)oxy]ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

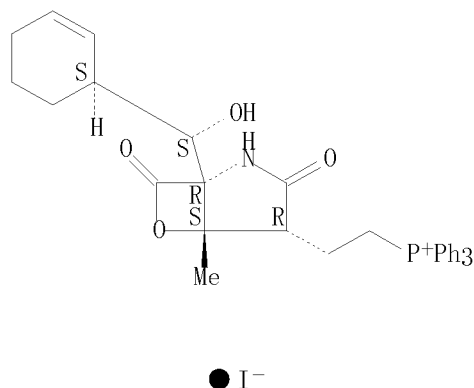
Absolute stereochemistry.



RN 1067236-86-5 CAPLUS

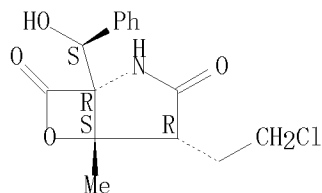
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



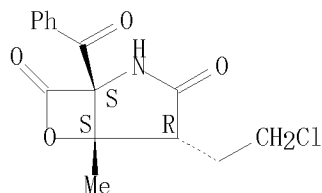
IT 1044999-00-9P 1057246-19-1P 1057246-20-4P  
1078724-62-5P 1078724-63-6P  
 RL: PRPH (Prophetic); SPN (Synthetic preparation); PREP (Preparation)  
 (heterocyclic compds. and analogs for treating infectious diseases)  
 RN 1044999-00-9 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA  
 INDEX NAME)

Absolute stereochemistry.



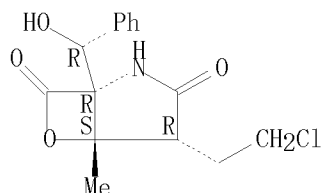
RN 1057246-19-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-benzoyl-4-(2-chloroethyl)-5-methyl-, (1S,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1057246-20-4 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA  
 INDEX NAME)

Absolute stereochemistry.

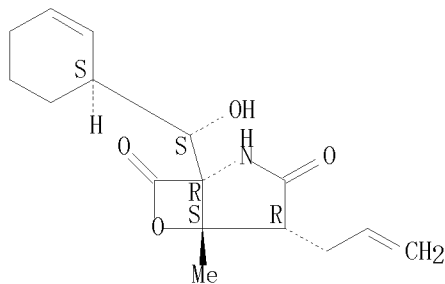


RN 1078724-62-5 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-(2-propen-1-yl)-,  
 (1R,4R,5S)- (CA INDEX NAME)



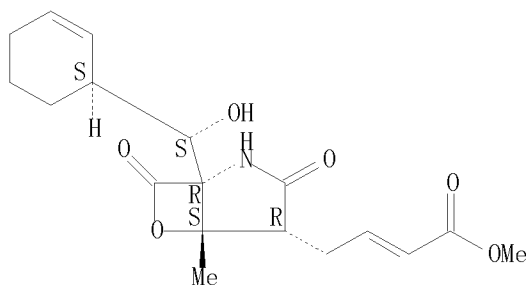
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



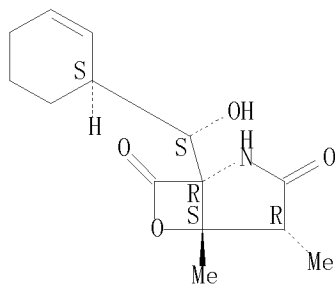
RN 1078724-63-6 CAPLUS  
 CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.  
 Double bond geometry unknown.



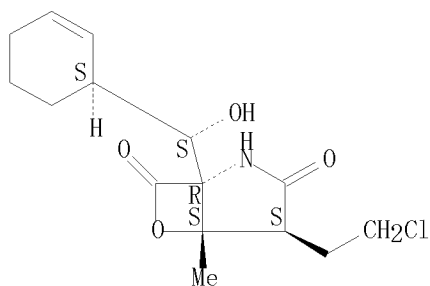
IT 823229-26-1P 872360-11-7P 872360-12-8P  
872360-13-9P 872360-16-2P  
 RL: PUR (Purification or recovery); PREP (Preparation)  
 (heterocyclic compds. and analogs for treating infectious diseases)  
 RN 823229-26-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R, 4R, 5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



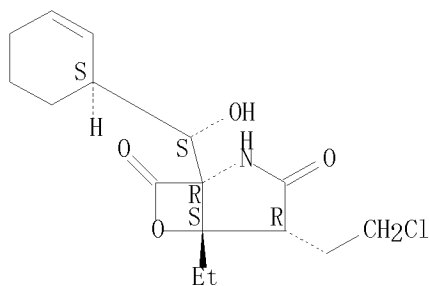
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 (1R, 4S, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



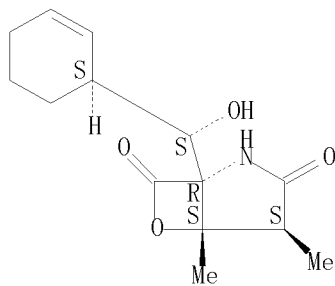
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 (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



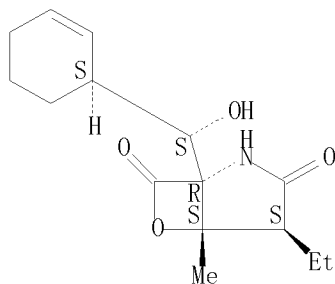
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 (CA INDEX NAME)

Absolute stereochemistry.



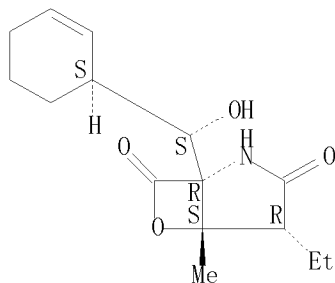
RN 872360-16-2 CAPLUS  
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 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R, 4S, 5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



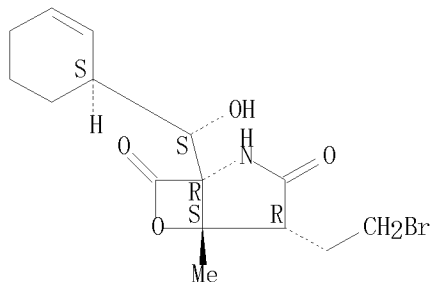
IT 863126-95-8P 872360-15-1P  
 RL: PUR (Purification or recovery); RCT (Reactant); PREP (Preparation);  
 RACT (Reactant or reagent)  
 (heterocyclic compds. and analogs for treating infectious diseases)  
 RN 863126-95-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



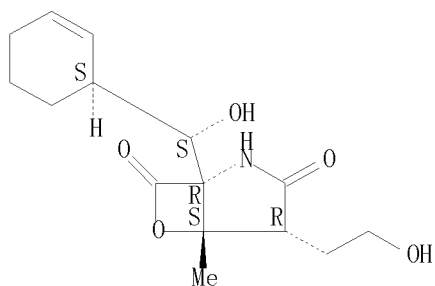
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 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



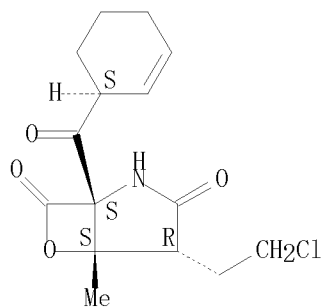
IT 823229-54-5P 872360-17-3P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
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 (heterocyclic compds. and analogs for treating infectious diseases)  
 RN 823229-54-5 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 872360-17-3 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
 (1S,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 76 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2008:1276294 CAPLUS

DOCUMENT NUMBER: 149:505521

TITLE: Leaving Groups Prolong the Duration of 20S Proteasome Inhibition and Enhance the Potency of Salinosporamides  
 AUTHOR(S): Manam, Rama Rao; McArthur, Katherine A.; Chao, Ta-Hsiang; Weiss, Jeffrey; Ali, Janid A.; Palombella, Vito J.; Groll, Michael; Lloyd, G. Kenneth; Palladino, Michael A.; Neuteboom, Saskia T. C.; Macherla, Venkat R.; Potts, Barbara C. M.

CORPORATE SOURCE: Nereus Pharmaceuticals Inc., San Diego, CA, 92121, USA  
 SOURCE: Journal of Medicinal Chemistry (2008), 51(21), 6711-6724

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 149:505521

ABSTRACT:

Salinosporamide A (NPI-0052) is a potent, monochlorinated 20S proteasome inhibitor in clin. trials for the treatment of cancer. To elucidate the role of the chlorine leaving group (LG), the authors synthesized analogs with a range of LG potentials and determined their IC50 values for inhibition of chymotrypsin-like (CT-L), trypsin-like (T-L), and caspase-like (C-L) activities of 20S proteasomes. Proteasome activity was also determined before and after attempted removal of the inhibitors by dialysis. Analogs bearing substituents with good LG potential exhibited the greatest potency and prolonged duration of proteasome inhibition, with no recovery after 24 h of dialysis. In contrast, activity was restored after ≤12 h in the case of non-LG analogs. Intermediate results were observed for fluorosalinosporamide, with poor LG potential. Kinetic studies indicate that Salinosporamide A acts as a classical slow, tight inhibitor of the CT-L, T-L, and C-L activities and that inhibition occurs via a two-step mechanism involving reversible recognition followed by rate-limiting formation of a covalent enzyme-inhibitor complex.

IT **823229-34-1P** **823229-54-5P**

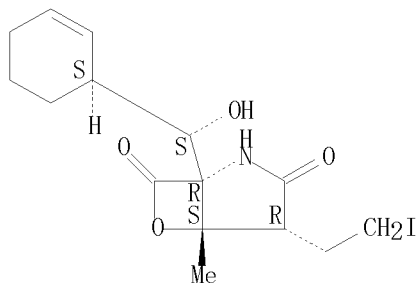
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(leaving groups prolong duration of 20S proteasome inhibition and enhance potency of prepared salinosporamides)

RN 823229-34-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

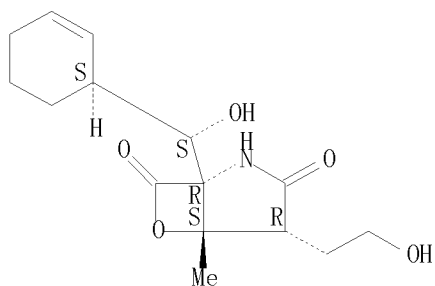
Absolute stereochemistry.



RN 823229-54-5 CAPLUS

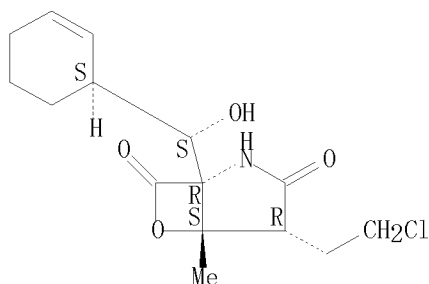
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



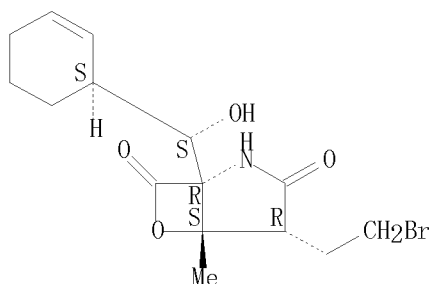
IT 437742-34-2, Salinosporamide A 872360-15-1  
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)  
 (leaving groups prolong duration of 20S proteasome inhibition and enhance potency of prepared salinosporamides)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



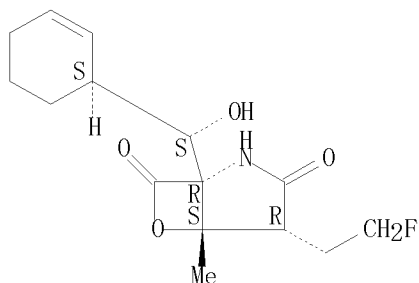
RN 872360-15-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 889457-14-1P 1057246-23-7P 1073241-43-6P  
1073241-49-2P  
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (leaving groups prolong duration of 20S proteasome inhibition and enhance potency of prepared salinosporamides)  
 RN 889457-14-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-fluoroethyl)-5-methyl-,  
 (1R, 4R, 5S)- (CA INDEX NAME)

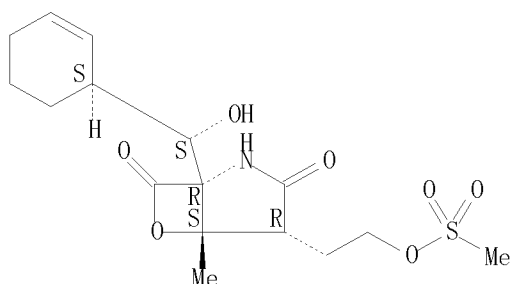
Absolute stereochemistry.



RN 1057246-23-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-  
[(methylsulfonyl)oxy]ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

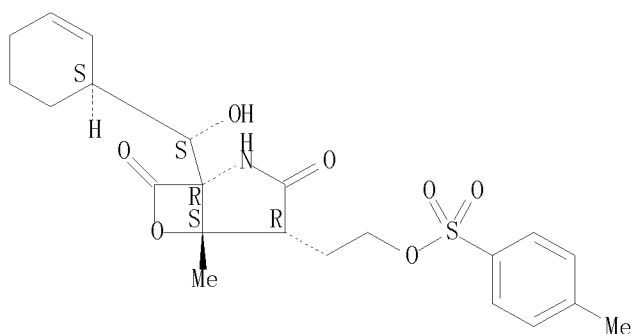
Absolute stereochemistry.



RN 1073241-43-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-[[4-  
methylphenyl)sulfonyl]oxy]ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

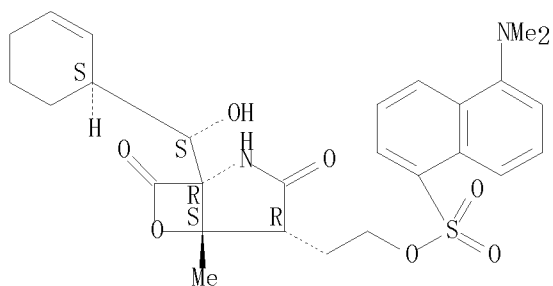
Absolute stereochemistry.



RN 1073241-49-2 CAPLUS

CN 1-Naphthalenesulfonic acid, 5-(dimethylamino)-,  
2-[(1R,4R,5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-  
dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA INDEX NAME)

Absolute stereochemistry.



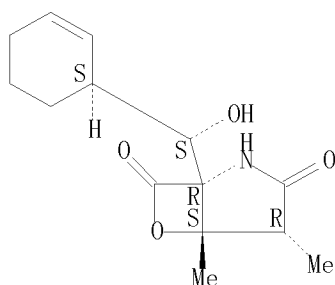
IT 823229-26-1 863126-95-8 872360-24-2

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (leaving groups prolong duration of 20S proteasome inhibition and enhance potency of prepared salinosporamides)

RN 823229-26-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4R,5S)- (CA INDEX NAME)

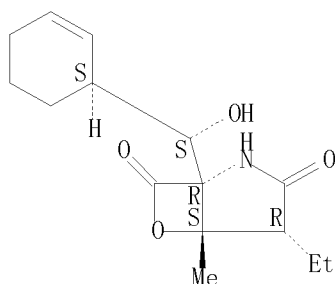
Absolute stereochemistry.



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

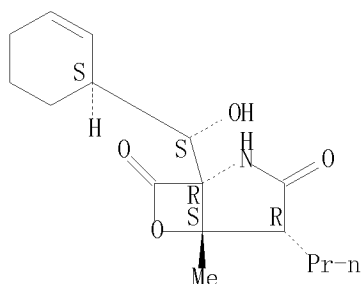


RN 872360-24-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.





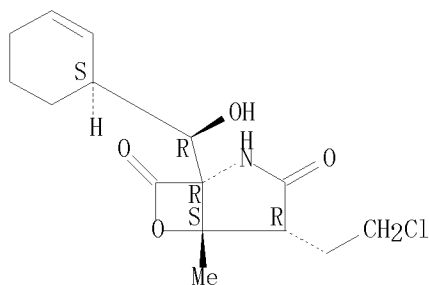
IT 872360-18-4 943542-56-1

RL: RCT (Reactant); RACT (Reactant or reagent)  
(leaving groups prolong duration of 20S proteasome inhibition and  
enhance potency of prepared salinosporamides)

RN 872360-18-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

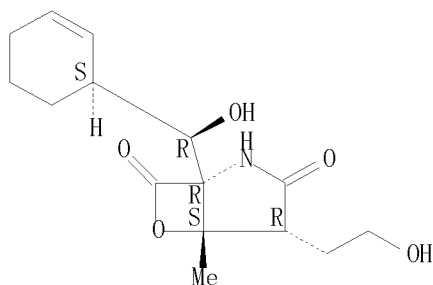
Absolute stereochemistry.



RN 943542-56-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
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(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



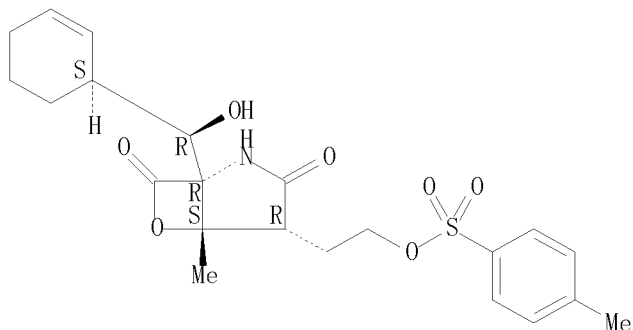
IT 1073241-44-7P 1073241-45-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(leaving groups prolong duration of 20S proteasome inhibition and  
enhance potency of prepared salinosporamides)

RN 1073241-44-7 CAPLUS

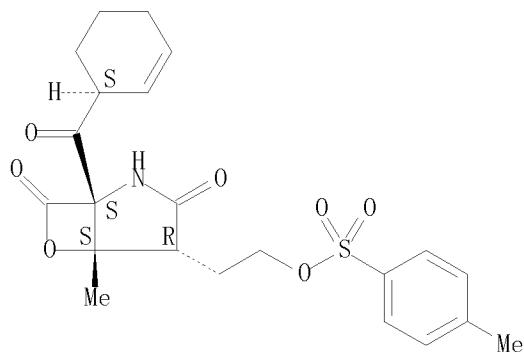
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-[[4-  
methylphenyl)sulfonyl]oxy]ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1073241-45-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-4-[2-[[4-  
 methylphenyl)sulfonyl]oxy]ethyl]-, (1S,4R,5S)- (CA INDEX NAME)

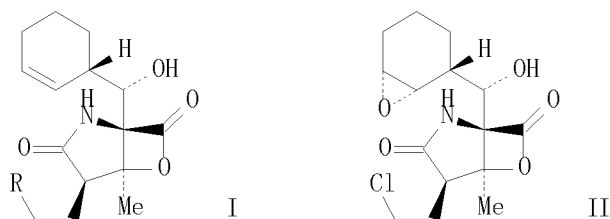
Absolute stereochemistry.



OS.CITING REF COUNT:	15	THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)
REFERENCE COUNT:	53	THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 77 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:1251205 CAPLUS  
 DOCUMENT NUMBER: 149:471258  
 TITLE: Preparation of salinosporamide A and analogous [3.2.0] bicyclic  $\beta$ -lactones for therapeutic use as proteasome inhibitors in combination with histone deacetylase inhibitors in the treatment of cancer  
 INVENTOR(S): Palladino, Michael; Anderson, Kenneth C.; Chauhan, Dharminder; Chandra, Joya; Mcconkey, David  
 PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA; Dana-Farber Cancer Institute; University of Texas M.D. Anderson Cancer Center  
 SOURCE: PCT Int. Appl., 226pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008124699	A1	20081016	WO 2008-US59592	20080407
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM PRIORITY APPLN. INFO.: US 2007-910623P P 20070406 US 2007-990895P P 20071128 OTHER SOURCE(S): MARPAT 149:471258 GRAPHIC IMAGE:				



# ABSTRACT:

Salinosporamide A I (R = Cl) and its analogs were prepared for therapeutic use as anticancer proteasome inhibitors. These salinosporamide analogs may be used in combination with one or more histone deacetylase inhibitors, such as (pyridin-3-yl)methyl 4-(2-aminophenylcarbamoyl)benzylcarbamate (MS 275), apicidin, (-)-depudecin, sodium butyrate, scriptaid, sirtinol, trichostatin A, valproic acid, tubacin, vorinostat and panobinostat. Salinosporamide A was prepared via a fermentation process using strain CNB476 or strain NPS21184. Salinosporamide A and related bicyclic  $\beta$ -lactones recovered from the fermentation process were subsequently converted to other  $\beta$ -lactone derivs., such as I (R = H, Br, iodo, Me) and II. The prepared  $\beta$ -lactones were tested extensively for anticancer anticancer activity including their effect on 20S proteasome. Pharmaceutical compns. containing the prepared salinosporamide analogs were discussed.

IT 1044999-00-9P 1057246-19-1P 1057246-20-4P  
1057246-22-6P 1057246-23-7P 1057246-24-8P  
1057246-25-9P

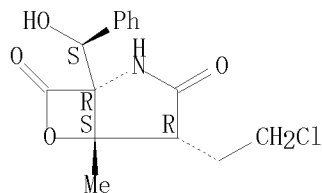
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of salinosporamide A and analogous [3.2.0] bicyclic  $\beta$ -lactones for therapeutic use as proteasome inhibitors in combination with histone deacetylase inhibitors in treatment of cancer)

RN 1044999-00-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

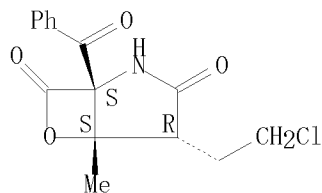
Absolute stereochemistry.



RN 1057246-19-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
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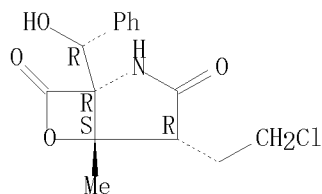
Absolute stereochemistry.



RN 1057246-20-4 CAPLUS

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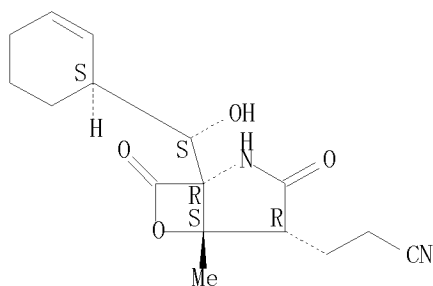
Absolute stereochemistry.



RN 1057246-22-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-4-propanenitrile,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

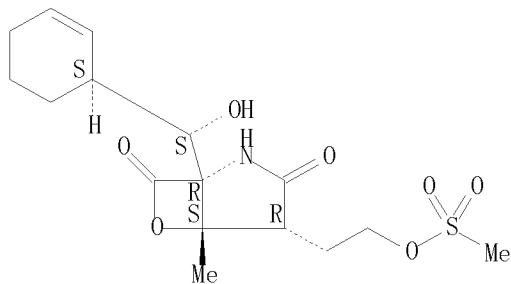


RN 1057246-23-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,

1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-[(methylsulfonyl)oxy]ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

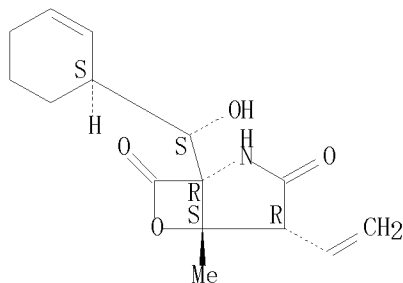
Absolute stereochemistry.



RN 1057246-24-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethenyl-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

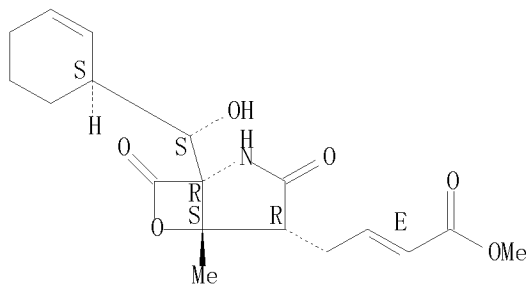


RN 1057246-25-9 CAPLUS

CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

Double bond geometry as shown.



IT **823229-34-1P** **872360-17-3P**

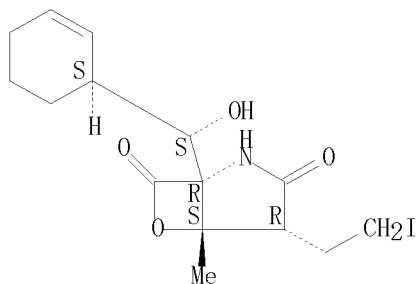
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of salinosporamide A and analogous [3.2.0] bicyclic  $\beta$ -lactones for therapeutic use as proteasome inhibitors in combination with histone deacetylase inhibitors in treatment of cancer)

RN 823229-34-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

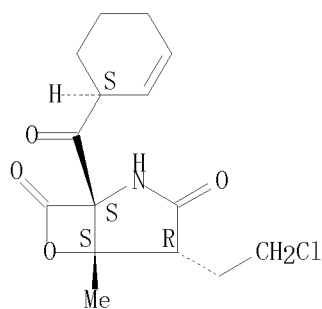
Absolute stereochemistry.



RN 872360-17-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
(1S,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



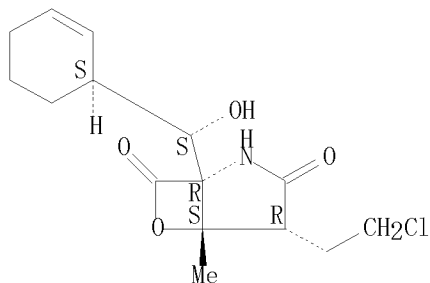
IT 437742-34-2P, Salinosporamide A 863126-95-8P  
872360-15-1P

RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT  
(Reactant); THU (Therapeutic use); BIOL (Biological study); PREP  
(Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of salinosporamide A and analogous [3.2.0] bicyclic  
β-lactones for therapeutic use as proteasome inhibitors in  
combination with histone deacetylase inhibitors in treatment of cancer)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

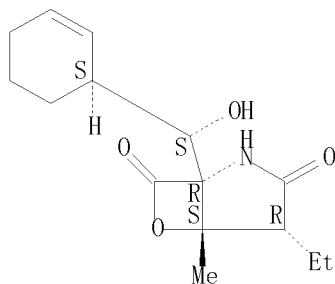
Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

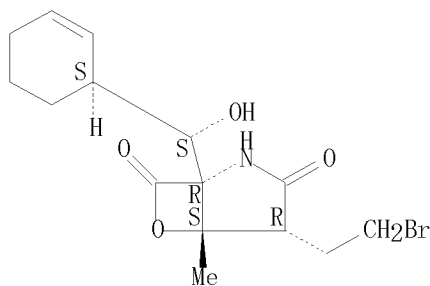
Absolute stereochemistry. Rotation (-).



RN 872360-15-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



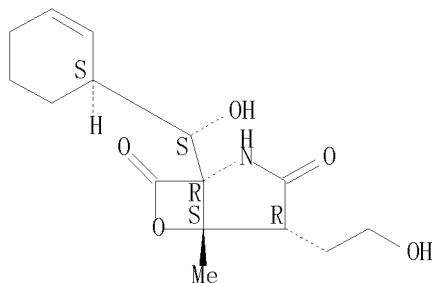
IT 823229-54-5P 823229-56-7P 872360-18-4P  
872360-22-0P 872360-23-1P 872360-24-2P

RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN  
(Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);  
PREP (Preparation); USES (Uses)  
(preparation of salinosporamide A and analogous [3.2.0] bicyclic  
β-lactones for therapeutic use as proteasome inhibitors in  
combination with histone deacetylase inhibitors in treatment of cancer)

RN 823229-54-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

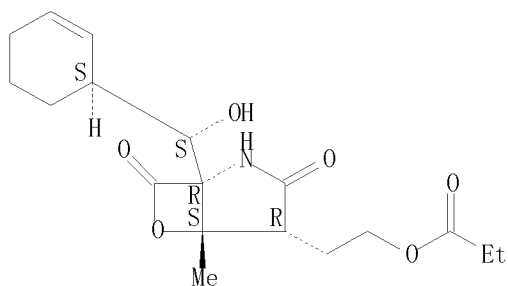
Absolute stereochemistry. Rotation (-).



RN 823229-56-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-(1-  
oxopropoxy)ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

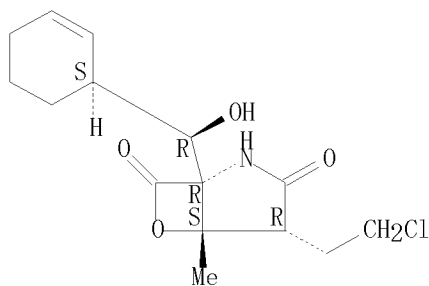
Absolute stereochemistry.



RN 872360-18-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

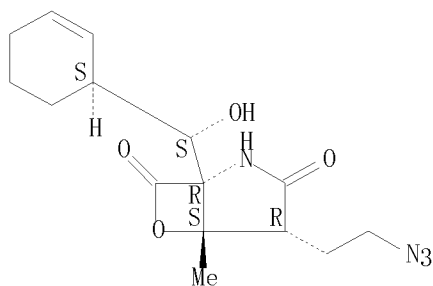
Absolute stereochemistry.



RN 872360-22-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-azidoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

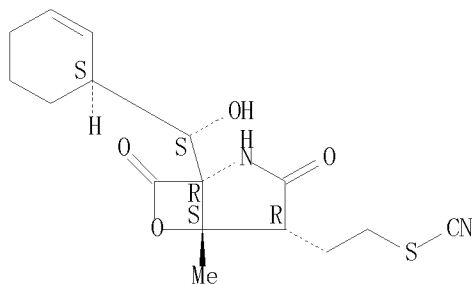


RN 872360-23-1 CAPLUS

CN Thiocyanic acid, 2-[(1R,4R,5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-  
5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA  
INDEX NAME)

Absolute stereochemistry.

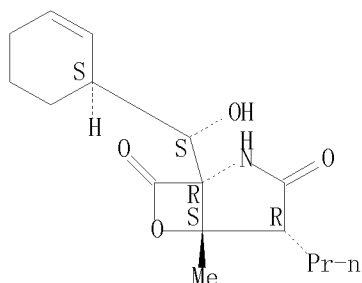




RN 872360-24-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 823229-26-1P 872360-11-7P 872360-12-8P  
872360-13-9P 872360-14-0P 872360-16-2P

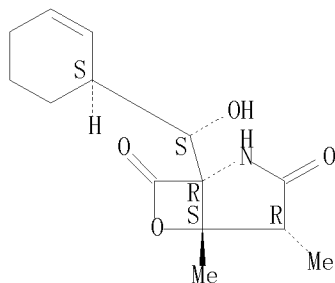
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
(Uses)

(preparation of salinosporamide A and analogous [3.2.0] bicyclic  
β-lactones for therapeutic use as proteasome inhibitors in  
combination with histone deacetylase inhibitors in treatment of cancer)

RN 823229-26-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R, 4R, 5S)-  
(CA INDEX NAME)

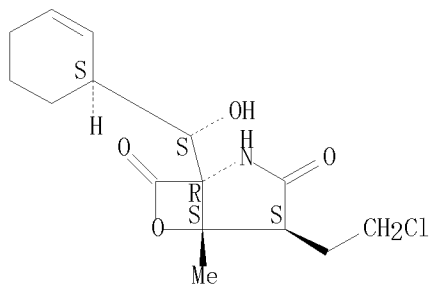
Absolute stereochemistry.



RN 872360-11-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R, 4S, 5S)- (CA INDEX NAME)

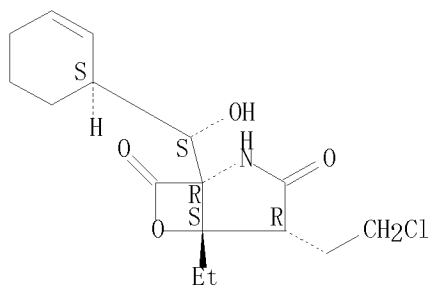
Absolute stereochemistry.



RN 872360-12-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-ethyl-,  
(1R,4R,5S)- (CA INDEX NAME)

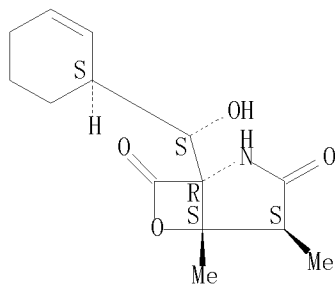
Absolute stereochemistry.



RN 872360-13-9 CAPLUS

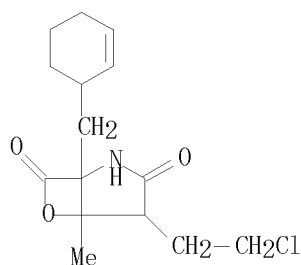
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4S,5S)-  
(CA INDEX NAME)

Absolute stereochemistry.



RN 872360-14-0 CAPLUS

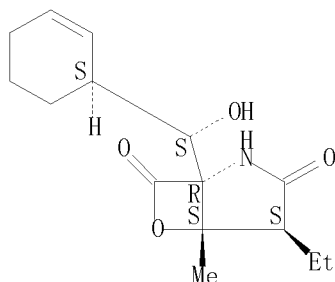
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-(2-cyclohexen-1-ylmethyl)-5-methyl- (CA INDEX NAME)



RN 872360-16-2 CAPLUS

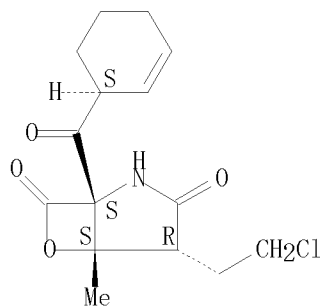
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4S,5S)-  
(CA INDEX NAME)

Absolute stereochemistry.



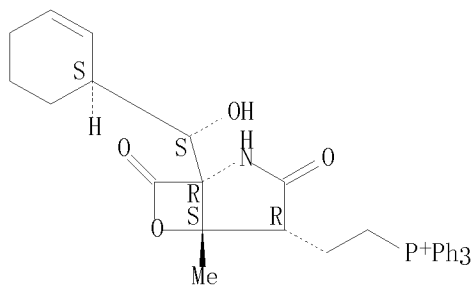
IT **872360-17-3P** **1067236-86-5P** **1070997-86-2P**  
 RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP  
 (Preparation); RACT (Reactant or reagent)  
 (preparation of salinosporamide A and analogous [3.2.0] bicyclic  
 $\beta$ -lactones for therapeutic use as proteasome inhibitors in  
 combination with histone deacetylase inhibitors in treatment of cancer)  
 RN 872360-17-3 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
 (1S,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1067236-86-5 CAPLUS  
 CN INDEX NAME NOT YET ASSIGNED

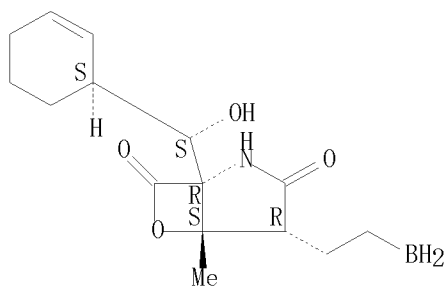
Absolute stereochemistry.



● I<sup>-</sup>

RN 1070997-86-2 CAPLUS  
 CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



OS.CITING REF COUNT:	1	THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT:	9	THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 78 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:1223087 CAPLUS  
 DOCUMENT NUMBER: 149:440342  
 TITLE: DR5-binding agonist antibodies for induction of  
 apoptosis in DR5 expressing cells and for treatment of  
 cancer and hepatitis C virus infections  
 INVENTOR(S): Ni, Jian; Gentz, Reiner L.; Yu, Guo-Liang; Rosen,  
 Craig A.  
 PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA  
 SOURCE: U.S. Pat. Appl. Publ., 138pp., Cont.-in-part of U.S.  
 Ser. No. 979,831.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 6  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20080248046	A1	20081009	US 2008-10106	20080118
CA 2644454	A1	19980924	CA 1998-2644454	19980317
EP 1788086	A1	20070523	EP 2007-1405	19980317
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 7803615	B1	20100928	US 1998-42583	19980317
US 6872568	B1	20050329	US 2000-565009	20000504
US 20020098550	A1	20020725	US 2001-5842	20011207
US 20040136951	A1	20040715	US 2003-648825	20030827
US 20050233958	A1	20051020	US 2004-979831	20041103
AU 2006246525	A1	20061221	AU 2006-246525	20061201
JP 2008081503	A	20080410	JP 2007-260427	20071003
PRIORITY APPLN. INFO.:			US 1997-40846P	P 19970317
			US 1997-54021P	P 19970729
			US 1998-42583	A2 19980317
			US 1999-132498P	P 19990504
			US 1999-133238P	P 19990507
			US 1999-148939P	P 19990813
			US 2000-565009	A2 20000504
			US 2002-406307P	P 20020828
			US 2002-413747P	P 20020927
			US 2003-648825	A2 20030827
			US 2004-551811P	P 20040311
			US 2004-608429P	P 20040910
			US 2004-979831	A2 20041103
			US 2007-885944P	P 20070122
			US 2007-990701P	P 20071128
			AU 1998-67635	A 19980317
			CA 1998-2285040	A3 19980317
			EP 1998-912966	A3 19980317
			JP 1998-540790	A3 19980317
			AU 2002-300603	A3 20020809

# ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

## ABSTRACT:

The present invention relates to novel Death Domain Containing Receptor-5 (DR5) proteins which are members of the tumor necrosis factor (TNF) receptor family, and have now been shown to bind TRAIL. In particular, antibodies with bind DR5 and act as agonists may be used to induce apoptosis in DR5-expressing cells. The DR5 agonist antibodies are used in combination with another agent, e.g., an alkylating agent, a PPAR $\gamma$  antagonist, a proteasome inhibitor, etc., to treat cancer. Addnl., they may be used in treating hepatitis C virus infections. Thus, human DR5 cDNA was cloned, sequenced, and expressed in E. coli, CHO and COS cells and the extracellular domain was produced in a baculovirus expression system. This extracellular domain bound to TRAIL and blocked TRAIL-induced apoptosis of MCF7 cells. Overexpression of DR5 in MCF7 breast carcinoma cells and in HeLa epitheloid carcinoma cells induced apoptosis in these cells.

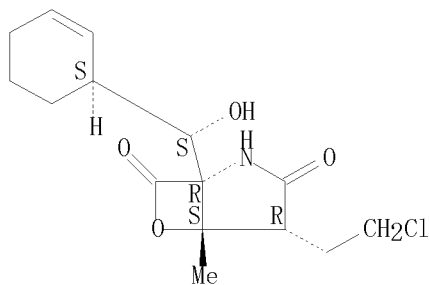
IT 437742-34-2, NPI-0052

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combination chemotherapy with; DR5-binding agonist antibodies for  
 induction of apoptosis in DR5 expressing cells and for treatment of  
 cancer and hepatitis C virus infections)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD  
(6 CITINGS)

L6 ANSWER 79 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2008:1211287 CAPLUS  
DOCUMENT NUMBER: 149:440403  
TITLE: Modulators for regulating autophagy, and therapeutic  
uses and combinations  
INVENTOR(S): Bradner, James Elliot; Shen, John Paul; Perlstein,  
Ethan Oren; Rubinsztein, David; Sarkar, Sovan;  
Schreiber, Stuart L.  
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA; Dana  
Farber Cancer Institute; Cambridge Enterprise Ltd.  
SOURCE: PCT Int. Appl., 159pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008122038	A1	20081009	WO 2008-US59129	20080402
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			

PRIORITY APPLN. INFO.: US 2007-909640P P 20070402

OTHER SOURCE(S): MARPAT 149:440403

ABSTRACT:

Autophagy is a cellular process by which cells cannibalize non-essential cellular elements such as organelles to generate metabolites, or in some cases, to cause cell death. The invention provides modulators of autophagy, which have been identified using a high-throughput phenotypic screen of over 3500 compds. These modulators are useful in treating diseases ranging from proliferative diseases to neurodegenerative diseases to infectious diseases to protein misfolding states. Furthermore, the invention provides the treatment of proliferative disease such as cancer with a combination of autophagy inhibitors and protein kinase inhibitors.

IT 437742-34-2, NPI-0052

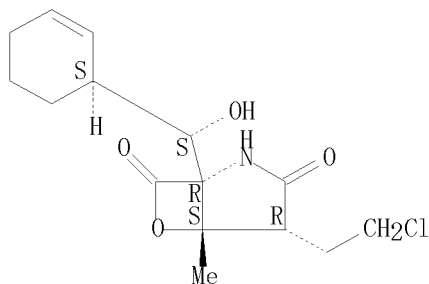
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(modulators for regulating autophagy, and therapeutic uses and combinations)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT:

7

THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT





L6 ANSWER 80 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:1197995 CAPLUS  
 DOCUMENT NUMBER: 150:343758  
 TITLE: Mechanisms of proteasome inhibitor action and resistance in cancer  
 AUTHOR(S): McConkey, David J.; Zhu, Keyi  
 CORPORATE SOURCE: Departments of Urology and Cancer Biology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030, USA  
 SOURCE: Drug Resistance Updates (2008), 11(4-5), 164-179  
 CODEN: DRUPFW; ISSN: 1368-7646  
 PUBLISHER: Elsevier Ltd.  
 DOCUMENT TYPE: Journal; General Review  
 LANGUAGE: English  
 ABSTRACT:

A review. Proteasome inhibitors (PIs), such as bortezomib, carfilzomib or NPI-0052, have excellent clin. activity in patients with multiple myeloma and mantle cell lymphoma, and they are currently being evaluated in combination with other agents in patients with solid tumors. Although they exert broad effects on cancer cells, their ability to (1) stabilize pro-apoptotic members of the BCL-2 family, (2) inhibit the two major pathways leading to NFκB activation, and (3) cause the build-up of misfolded proteins appear to be particularly important. In addition, PIs may disrupt tumor-stromal interactions that drive NFκB activation and angiogenesis and in such a way sensitize cancer cells to other agents. Still, drug resistance ultimately emerges in all tumors that initially respond to PIs. This review provides an overview of the current thinking about how PIs may kill cancer cells exemplified for pancreatic cancer and the possible mechanisms involved in resistance to PIs.

IT **437742-34-2**, NPI-0052

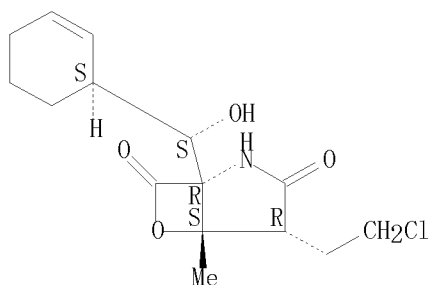
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(bortezomib, carfilzomib or NPI-0052 may disrupt tumor-stromal interactions that drive NFκB activation, angiogenesis and its initial response to tumor may lead to drug resistance in patient with multiple myeloma and mantle cell lymphoma)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 47 THERE ARE 47 CAPLUS RECORDS THAT CITE THIS RECORD (47 CITINGS)  
 REFERENCE COUNT: 181 THERE ARE 181 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L6 ANSWER 81 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:1191409 CAPLUS  
 DOCUMENT NUMBER: 149:417697  
 TITLE: Death domain containing receptor DR4 and methods for  
 inducing apoptosis and treating cancer with DR4  
 agonist antibodies  
 INVENTOR(S): Ni, Jian; Rosen, Craig A.; Pan, James G.; Gentz,  
 Reiner L.; Dixit, Vishva M.  
 PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA; The Regents of the  
 University of Michigan  
 SOURCE: U.S. Pat. Appl. Publ., 146pp., Cont.-in-part of U.S.  
 Ser. No. 76,187.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 6  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20080241155	A1	20081002	US 2008-10108	20080118
US 6342363	B1	20020129	US 1998-13895	19980127
EP 1862548	A1	20071205	EP 2007-9954	19980127
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 6461823	B1	20021008	US 1999-448868	19991124
US 6433147	B1	20020813	US 2000-565918	20000505
US 20030036168	A1	20030220	US 2002-226296	20020823
US 6943020	B2	20050913		
US 20030073187	A1	20030417	US 2002-226318	20020823
US 7060272	B2	20060613		
US 20040136950	A1	20040715	US 2003-648786	20030827
US 20050112090	A9	20050526		
US 7452538	B2	20081118		
US 20050244857	A1	20051103	US 2005-76187	20050310
US 7476384	B2	20090113		
JP 2007326879	A	20071220	JP 2007-230847	20070905
PRIORITY APPLN. INFO.:				
			US 1997-35722P	P 19970128
			US 1997-37829P	P 19970205
			US 1998-13895	A2 19980127
			US 1999-132922P	P 19990506
			US 2000-565918	A2 20000505
			US 2002-406922P	P 20020830
			US 2002-413861P	P 20020927
			US 2003-648786	A2 20030827
			US 2004-551768P	P 20040311
			US 2004-608469P	P 20040910
			US 2005-76187	A2 20050310
			US 2007-885971P	P 20070122
			US 2007-990687P	P 20071128
			EP 1998-904690	A3 19980127
			JP 1998-532198	A3 19980127
			US 1999-448868	A1 19991124

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

#### ABSTRACT:

The present invention relates to death domain-containing receptor 4 (DR4) proteins which are members of the tumor necrosis factor receptor family. A method for inducing apoptosis and treating cancer of a DR4-expressing cell comprising contacting the cell with an agonist antibody which binds to the extracellular domain of DR4 is disclosed. Thus, expts. are described which indicate that DR4 is an apoptosis-inducing receptor which binds TRAIL.

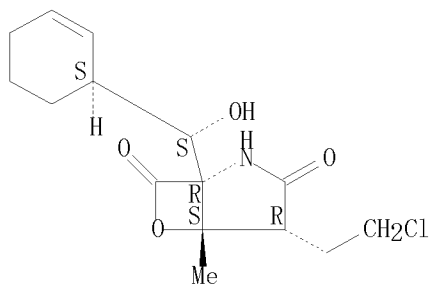
IT 437742-34-2, NPI 0052

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combination chemotherapy with; death domain containing receptor DR4 and  
 methods for inducing apoptosis and treating cancer with DR4 agonist  
 antibodies)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 8

THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD  
(26 CITINGS)

L6 ANSWER 82 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2008:1108503 CAPLUS  
DOCUMENT NUMBER: 150:228996  
TITLE: Progress in drug therapy for multiple myeloma  
AUTHOR(S): Yang, Shun'e; Zhao, Bing  
CORPORATE SOURCE: Department of Medical Oncology, Tumor Hospital of  
Xinjiang Medical University, Urumqi, 830011, Peop.  
Rep. China  
SOURCE: Chinese Journal of Clinical Oncology (2008), 5(4),  
251-257  
CODEN: CJC0B4; ISSN: 1672-7118  
PUBLISHER: Tianjin Cancer Institute and Hospital  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

A review. Multiple myeloma remains incurable with conventional treatments. However, new active drugs, including the immunomodulatory agents, thalidomide and lenalidomide, and the proteasome inhibitors bortezomib and NPI-0052, and other targeted therapies, have shown promising anti-myeloma activity. These agents represent a new generation of treatments for multiple myeloma that affect both specific intracellular signaling pathways and the tumor microenvironment. This review therefore focuses on the extensive clin. data available from studies of these drugs in the treatment of newly diagnosed, refractory and relapsed multiple myeloma.

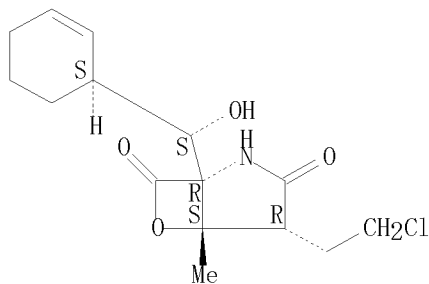
IT **437742-34-2**, NPI-0052

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(NPI-0052 therapy may help in tumor treatment by affecting  
intracellular signaling pathway, tumor microenvironment in patient with  
multiple myeloma)

RN 437742-34-2 CAPLUS

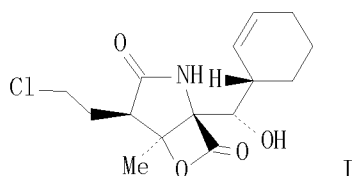
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 83 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:1085637 CAPLUS  
 DOCUMENT NUMBER: 149:402087  
 TITLE: Total Synthesis of Salinosporamide A  
 AUTHOR(S): Fukuda, Takeo; Sugiyama, Kouhei; Arima, Shiho;  
 Harigaya, Yoshihiro; Nagamitsu, Tohru; Omura, Satoshi  
 CORPORATE SOURCE: School of Pharmacy, Kitasato University, 5-9-1  
 Shirokane, Minato-ku, Tokyo, 108-8641, Japan  
 SOURCE: Organic Letters (2008), 10(19), 4239-4242  
 CODEN: ORLEF7; ISSN: 1523-7060  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 149:402087  
 GRAPHIC IMAGE:



# ABSTRACT:

The total synthesis of salinosporamide A (I) has been achieved through enzymic desymmetrization, diastereoselective aldol reaction, intramol. aldol reaction, and intermol. Reformatsky-type reaction followed by 1,4-reduction as key reactions.

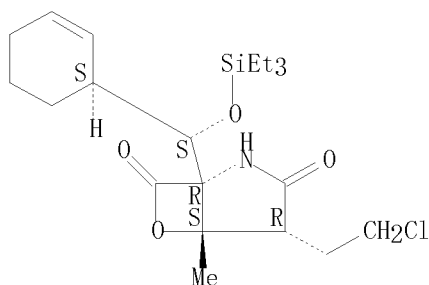
IT **1064062-25-4P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (asym. synthesis of salinosporamide A)

RN 1064062-25-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-yl]-(triethylsilyl)methyl-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



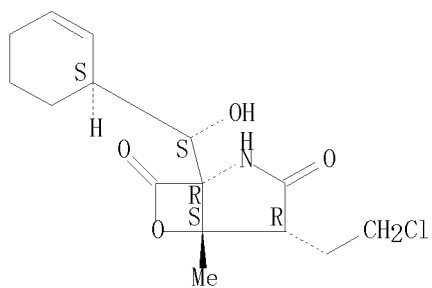
IT **437742-34-2P**

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (asym. synthesis of salinosporamide A)

RN 437742-34-2 CAPLUS

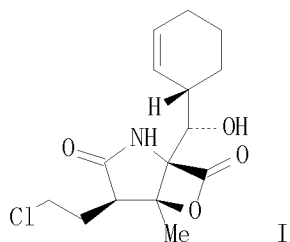
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-yl]hydroxymethyl-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS  
RECORD (18 CITINGS)  
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 84 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:990362 CAPLUS  
 DOCUMENT NUMBER: 149:448077  
 TITLE: Entry to heterocycles based on indium-catalyzed  
 Conia-ene reactions: asymmetric synthesis of  
 (-)-salinosporamide A  
 AUTHOR(S): Takahashi, Keisuske; Midori, Michiko; Kawano, Kei;  
 Ishihara, Jun; Hatakeyama, Susumi  
 CORPORATE SOURCE: Graduate School of Biomedical Sciences, Nagasaki  
 University, 1-14 Bnkyo-machi, Nagasaki, 852-8521,  
 Japan  
 SOURCE: Angewandte Chemie, International Edition (2008),  
 47(33), 6244-6246  
 CODEN: ACIEF5; ISSN: 1433-7851  
 PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 149:448077  
 GRAPHIC IMAGE:



# ABSTRACT:

The In(OTf)<sub>3</sub>-catalyzed cyclization of nitrogen- and oxygen-tethered acetylenic malonic esters gives five- to seven-membered heterocycles in moderate to excellent yields. The asym. synthesis of (-)-salinosporamide A (I) illustrates the synthetic utility of the method.

# IT 823229-54-5P

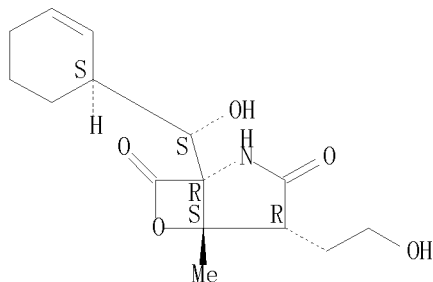
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(entry to heterocycles based on indium-catalyzed Conia-ene reactions and its application for the asym. synthesis of (-)-salinosporamide A)

RN 823229-54-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



# IT 437742-34-2P

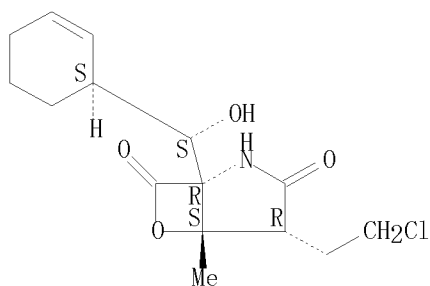
RL: SPN (Synthetic preparation); PREP (Preparation)

(entry to heterocycles based on indium-catalyzed Conia-ene reactions and its application for the asym. synthesis of (-)-salinosporamide A)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	35	THERE ARE 35 CAPLUS RECORDS THAT CITE THIS RECORD (35 CITINGS)
REFERENCE COUNT:	41	THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 85 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2008:976367 CAPLUS

DOCUMENT NUMBER: 150:205862

TITLE: Proteasome Inhibition Activates Epidermal Growth Factor Receptor (EGFR) and EGFR-Independent Mitogenic Kinase Signaling Pathways in Pancreatic Cancer Cells  
AUTHOR(S): Sloss, Callum M.; Wang, Fang; Liu, Rong; Xia, Lijun; Houston, Michael; Ljungman, David; Palladino, Michael A.; Cusack, James C., Jr.

CORPORATE SOURCE: Division of Surgical Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, 02114, USA

SOURCE: Clinical Cancer Research (2008), 14(16), 5116-5123  
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

PURPOSE: In the current study, we investigate the activation of antiapoptotic signaling pathways in response to proteasome inhibitor treatment in pancreatic cancer and evaluate the use of concomitant inhibition of these pathways to augment proteasome inhibitor treatment responses. Exptl. Design: Pancreatic cancer cell lines and mouse flank xenografts were treated with proteasome inhibitor alone or in combination with chemotherapeutic compds. (gemcitabine, erlotinib, and bevacizumab), induction of apoptosis and effects on tumor growth were assessed. The effect of bortezomib (a first-generation proteasome inhibitor) and NPI-0052 (a second-generation proteasome inhibitor) treatment on key pancreatic mitogenic and antiapoptotic pathways [epidermal growth factor receptor, extracellular signal-regulated kinase, and phosphoinositide-3-kinase (PI3K)/AKT] was determined and the ability of inhibitors of these pathways to enhance the effects of proteasome inhibition was assessed in vitro and in vivo.

RESULTS: Our data showed that proteasome inhibitor treatment activates antiapoptotic and mitogenic signaling pathways (epidermal growth factor receptor, extracellular signal-regulated kinase, c-Jun-NH2-kinase, and PI3K/AKT) in pancreatic cancer. Addnl., we found that activation of these pathways impairs tumor response to proteasome inhibitor treatment and inhibition of the c-Jun-NH2-kinase and PI3K/AKT pathways increases the antitumor effects of proteasome inhibitor treatment. CONCLUSION: These preclin. studies suggest that targeting proteasome inhibitor-induced antiapoptotic signaling pathways in combination with proteasome inhibition may augment treatment response in highly resistant solid organ malignancies. Further evaluation of these novel treatment combinations in clin. trials is warranted.

IT 437742-34-2, NPI-0052

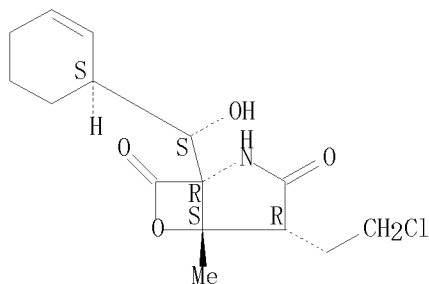
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(proteasome inhibition activates epidermal growth factor receptor and EGFR-independent mitogenic kinase signaling pathways in pancreatic cancer cells)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 24 THERE ARE 24 CAPLUS RECORDS THAT CITE THIS RECORD (24 CITINGS)

REFERENCE COUNT:

42      THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 86 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2008:975261 CAPLUS

DOCUMENT NUMBER: 149:288945

TITLE: Preparation and methods of using macrocyclic modulators of the ghrelin receptor

INVENTOR(S): Hoveyda, Hamid; Fraser, Graeme L.; Benakli, Kamel; Beauchemin, Sophie; Brassard, Martin; Drutz, David; Marsault, Eric; Ouellet, Luc; Peterson, Mark L.; Wang, Zhigang

PATENT ASSIGNEE(S): Tranzyme Pharma Inc., Can.

SOURCE: U.S. Pat. Appl. Publ., 178pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

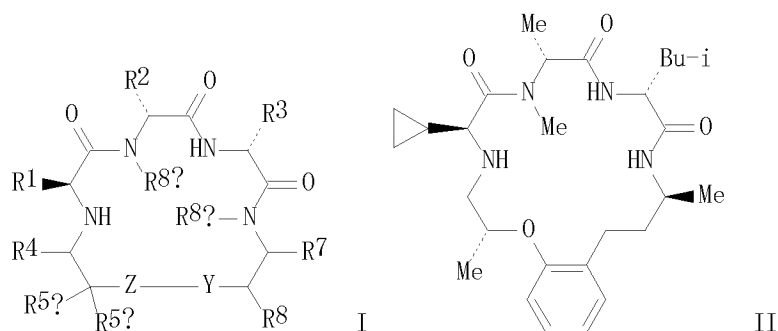
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20080194672	A1	20080814	US 2008-28611	20080208
AU 2008241532	A1	20081030	AU 2008-241532	20080208
CA 2677399	A1	20081030	CA 2008-2677399	20080208
WO 2008130464	A1	20081030	WO 2008-US1754	20080208
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
KR 2009107088	A	20091012	KR 2009-7018709	20080208
EP 2118080	A1	20091118	EP 2008-799889	20080208
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS				
JP 2010518090	T	20100527	JP 2009-549129	20080208
MX 2009008574	A	20091209	MX 2009-8574	20090810
IN 2009DN05639	A	20100507	IN 2009-DN5639	20090831
CN 101657436	A	20100224	CN 2008-80010587	20090928
PRIORITY APPLN. INFO.:				US 2007-889163P P 20070209
				WO 2008-US1754 W 20080208

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 149:288945

GRAPHIC IMAGE:



## ABSTRACT:

The invention provides novel conformationally-defined macrocyclic compds. I [R1 = (un)substituted cycloalkyl, lower alkyl; R2 = (un)substituted lower alkyl; R3 = alkyl, alkyl substituted with hydroxy or carboxy and alkyl substituted with aryl; R4, R5a, R5b, R6, R7, R8a, R8b = independently H, lower alkyl; Y = CR9aR9b; R9a, R9b = independently H, lower alkyl; Z = certain ring structures]

and their pharmaceutically acceptable salts that have been demonstrated to be selective modulators, particularly agonists, of the ghrelin receptor (growth hormone secretagogue receptor, GHS-R1a and subtypes, isoforms and variants) and are useful alone or in combination with other therapeutics as medicaments for the treatment and prevention of metabolic and/or endocrine disorders, gastrointestinal disorders, cardiovascular disorders, obesity, etc. Thus, cyclic peptide II was prepared by a multiple-step sequence involving peptide coupling and cyclization and evaluated for biol. activity, e.g., it caused a significant increase (41%) in gastric emptying in rats at a dose of 10 mg/kg after oral administration.

IT **437742-34-2**, Salinosporamide A

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

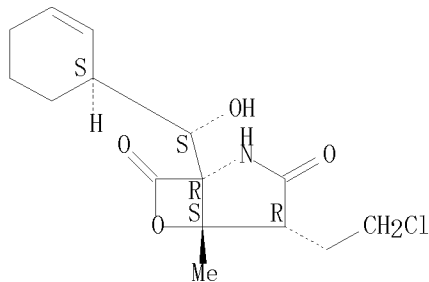
(Biological study); USES (Uses)

(novel conformationally-defined macrocyclic compds. as selective modulators of ghrelin receptors useful in mono- and combination therapy and prevention of diseases)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 87 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2008:946308 CAPLUS  
DOCUMENT NUMBER: 149:231630  
TITLE: Lyophilized formulations of salinosporamide a  
INVENTOR(S): Potts, Barbara; Singh, Ramsharan; Chu, Jan-Jon; Mai,  
Bao Viet; Reddinger, Natasha; Billstrom, Cheryl  
PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
SOURCE: PCT Int. Appl., 61pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008095195	A2	20080807	WO 2008-US52956	20080204
WO 2008095195	A3	20090416		
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
US 20080188544	A1	20080807	US 2008-25679	20080204
US 7824698	B2	20101102		

PRIORITY APPLN. INFO.: US 2007-888025P P 20070202  
US 2007-986891P P 20071109

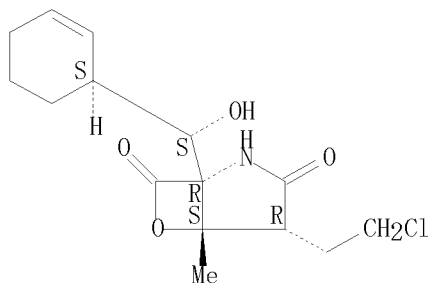
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

ABSTRACT:

Lyophilized formulations comprising Salinosporamide A or analogs thereof are provided. In some aspects, lyophilized formulations comprising Salinosporamide A or analogs thereof and bulking agents are provided. Also provided are methods of lyophilizing Salinosporamide A or analogs thereof. In some aspects, a solvent or co-solvent system is utilized. Also provided are methods of administering Salinosporamide A or analogs thereof to patients.

IT **437742-34-2**, Salinosporamide a  
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
(lyophilized formulations of salinosporamide a)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
(1 CITINGS)

L6 ANSWER 88 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:916140 CAPLUS  
 DOCUMENT NUMBER: 149:215945  
 TITLE: Combination therapy of cancer with romidepsin and a  
 proteasome inhibitor  
 INVENTOR(S): Keegan, Mitchell; Grant, Steven  
 PATENT ASSIGNEE(S): Gloucester Pharmaceuticals, USA  
 SOURCE: PCT Int. Appl., 68pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008091620	A2	20080731	WO 2008-US850	20080123
WO 2008091620	A3	20080918		
W:	AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
AU 2008209555	A1	20080731	AU 2008-209555	20080123
CA 2676387	A1	20080731	CA 2008-2676387	20080123
US 20090105200	A1	20090423	US 2008-9867	20080123
EP 2117556	A2	20091118	EP 2008-713230	20080123
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR			
JP 2010516767	T	20100520	JP 2009-547278	20080123
MX 2009007777	A	20091216	MX 2009-7777	20090721
PRIORITY APPLN. INFO. :			US 2007-886169P	P 20070123
			US 2007-5774P	P 20071207
			WO 2008-US850	W 20080123

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

#### ABSTRACT:

The invention provides a combination therapy for treating cancer and other neoplasms including romidepsin and a proteasome inhibitor. When administered together, romidepsin and a proteasome inhibitor (e.g., bortezomib) interact synergistically to selectively kill malignant cells at low (nanomolar) concns. The effect is particularly pronounced in malignant hematol. cells (e.g., leukemia, lymphoma, multiple myeloma). The combination has also been found useful in treating bortezomib-resistant cancers and steroid-resistant cancers. The invention provides methods of killing malignant cells in vitro and in vivo. Pharmaceutical compns., prepns., and kits including romidepsin and a proteasome inhibitor are also provided. In addition, other compds. such as steroids can be administered.

IT 437742-34-2, Salinosporamide A

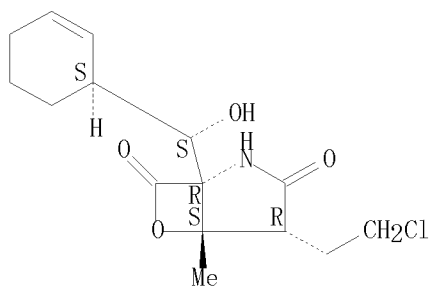
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combination therapy of cancer with romidepsin and a proteasome inhibitor and combination with other agents such as steroids)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 89 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2008:885264 CAPLUS  
DOCUMENT NUMBER: 149:193449  
TITLE: The ubiquitin proteasome system  
AUTHOR(S): Fuchs, Dominik; Berges, Carsten; Naujokat, Cord  
CORPORATE SOURCE: Institut fuer Immunologie, Universitaetsklinikum  
Heidelberg, Heidelberg, Germany  
SOURCE: Biologie in Unserer Zeit (2008), 38(3), 168-174  
CODEN: BLUZAR; ISSN: 0045-205X  
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: German

ABSTRACT:  
A review on discovery and relevance of the ubiquitin system, the 26S proteasome, regulation of cellular functions by the 26S proteasome system, and the therapeutic use of proteasome inhibitors.

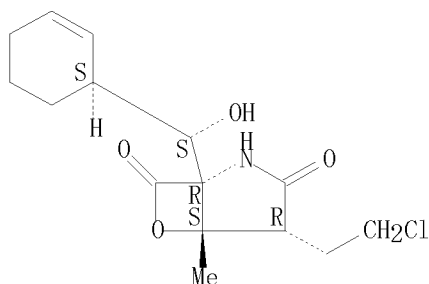
IT 437742-34-2, NPI-0052

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(ubiquitin proteasome system and its therapeutic uses)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

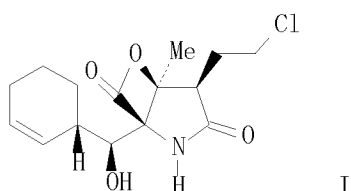


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
(1 CITINGS)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 90 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:855206 CAPLUS  
 DOCUMENT NUMBER: 149:355589  
 TITLE: A concise and straightforward total synthesis of  
 ( $\pm$ )-salinosporamideA, based on a biosynthesis  
 model  
 AUTHOR(S): Mulholland, Nicholas P.; Pattenden, Gerald; Walters,  
 Iain A. S.  
 CORPORATE SOURCE: School of Chemistry, University of Nottingham,  
 Nottingham, NG7 2RD, UK  
 SOURCE: Organic & Biomolecular Chemistry (2008), 6(15),  
 2782-2789  
 CODEN: OBCRAK; ISSN: 1477-0520  
 PUBLISHER: Royal Society of Chemistry  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 149:355589  
 GRAPHIC IMAGE:



# ABSTRACT:

A 14-step total synthesis of ( $\pm$ )-salinosporamideA (I), a potent inhibitor of the 20S proteasome isolated from the marine bacterium *Salinospora tropica*, is described. The synthesis is based on a diastereoselective intramol. aldolization of a substituted  $\beta$ -keto amide intermediate derived from a  $\beta$ -keto acid and an  $\alpha$ -amino malonate, leading to the pyrrolidinone ring II in the natural product. This synthetic approach closely mimics the origin of the pyrrolidinone ring in salinosporamide A in vivo. Another key feature of the total synthesis is a regioselective reduction of a malonate derivative to the key aldehyde intermediate, using Super-hydride.

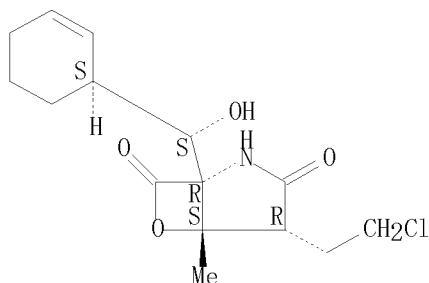
# IT 909569-43-3P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (stereoselective synthesis of ( $\pm$ )-salinosporamideA based on a  
 biosynthesis model)

RN 909569-43-3 CAPLUS

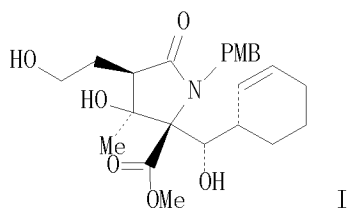
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1S,4S,5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



OS.CITING REF COUNT: 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS  
 RECORD (14 CITINGS)  
 REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 91 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2008:850668 CAPLUS  
DOCUMENT NUMBER: 149:332080  
TITLE: Formal synthesis of salinosporamide A using a  
nickel-catalyzed reductive aldol  
cyclization-lactonization as a key step  
AUTHOR(S): Villanueva Margalef, Isabel; Rupnicki, Leszek; Lam,  
Hon Wai  
CORPORATE SOURCE: School of Chemistry, University of Edinburgh,  
Edinburgh, EH9 3JJ, UK  
SOURCE: Tetrahedron (2008), 64(34), 7896-7901  
CODEN: TETRAB; ISSN: 0040-4020  
PUBLISHER: Elsevier Ltd.  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
OTHER SOURCE(S): CASREACT 149:332080  
GRAPHIC IMAGE:

**ABSTRACT:**

Application of a sequential nickel-catalyzed reductive aldol cyclization-lactonization reaction to prepare the compound I in a short formal synthesis of salinosporamide A, a potent 20S proteasome inhibitor and anti-cancer compound, is described.

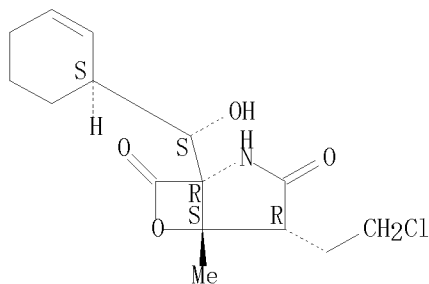
IT **437742-34-2P**, Salinosporamide A

RL: SPN (Synthetic preparation); PREP (Preparation)  
(asym. formal synthesis of salinosporamide A using a nickel-catalyzed reductive aldol cyclization-lactonization as a key step)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD  
(3 CITINGS)  
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 92 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:805271 CAPLUS  
 DOCUMENT NUMBER: 149:102818  
 TITLE: Salt formulations for the fermentative production of  
 salinopsporamides by *Salinispora tropica*  
 INVENTOR(S): Lam, Kin Sing; Tsueng, Ginger  
 PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
 SOURCE: U.S. Pat. Appl. Publ., 52 pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20080160590	A1	20080703	US 2007-860491	20070924
PRIORITY APPLN. INFO.:			US 2006-846774P	P 20060922
			US 2007-949147P	P 20070711
			US 2007-952349P	P 20070727
			US 2007-952368P	P 20070727

# ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 149:102818; MARPAT 149:102818

## ABSTRACT:

Growth medium are disclosed for use in fermenting a marine microorganism. The medium comprise potassium, calcium, strontium, borate and fluoride at specific concns. Alternatively, the growth medium comprises cobalt at specified concns. or comprises vitamin B12 at specified concns. Methods of producing certain desired compound by fermentation of a marine microorganism are also disclosed.

IT **863126-95-8P**, Salinosporamide B

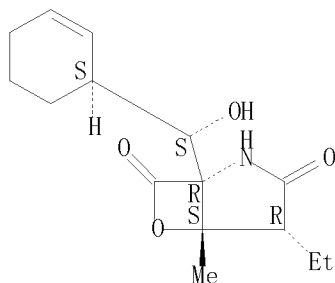
RL: BMF (Bioindustrial manufacture); BYP (Byproduct); PRP (Properties);  
 PUR (Purification or recovery); BIOL (Biological study); PREP  
 (Preparation)

(salt formulations for fermentative production of salinopsporamides by  
*Salinispora tropica*)

RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **437742-34-2P**, Salinosporamide A **823229-26-1P**

**872360-12-8P** **872360-13-9P** **872360-15-1P**

**872360-16-2P** **932739-03-2P**

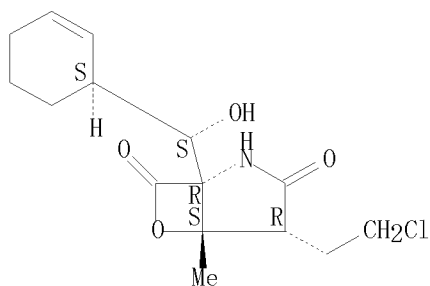
RL: BMF (Bioindustrial manufacture); PRP (Properties); PUR (Purification  
 or recovery); BIOL (Biological study); PREP (Preparation)

(salt formulations for fermentative production of salinopsporamides by  
*Salinispora tropica*)

RN 437742-34-2 CAPLUS

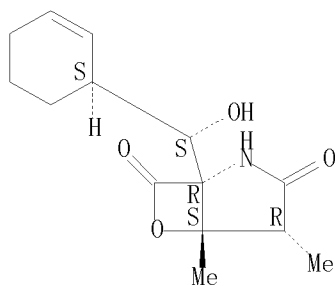
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



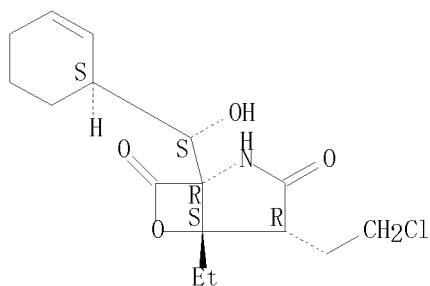
RN 823229-26-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



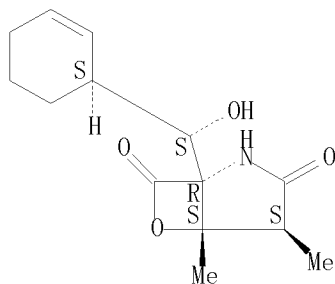
RN 872360-12-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-ethyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



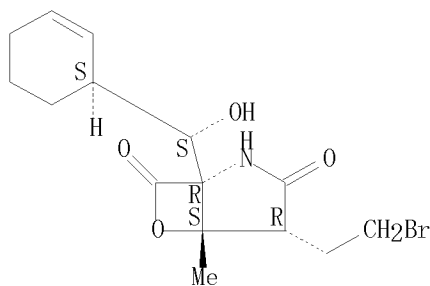
RN 872360-13-9 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4S,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



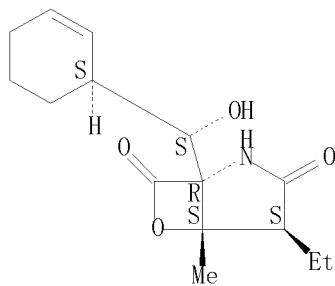
RN 872360-15-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



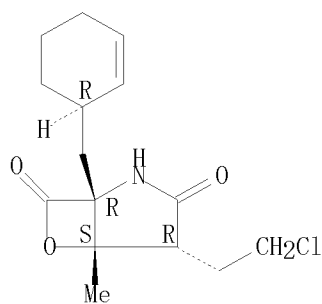
RN 872360-16-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4S,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



RN 932739-03-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(1R)-2-cyclohexen-1-ylmethyl]-5-methyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



IT **872360-11-7P**, NPI 2065

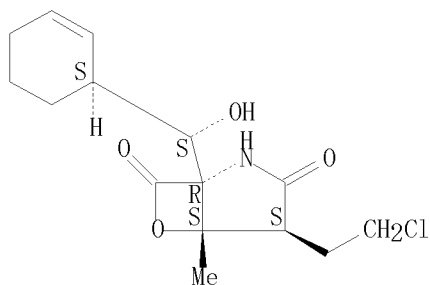
RL: BYP (Byproduct); PREP (Preparation)

(salt formulations for fermentative production of salinopsporamides by *Salinispora tropica*)

RN 872360-11-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 93 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:747557 CAPLUS  
 DOCUMENT NUMBER: 149:282501  
 TITLE: Marine actinomycetes: a new source of compounds  
 against the human malaria parasite  
 AUTHOR(S): Prudhomme, Jacques; McDaniel, Eric; Ponts, Nadia;  
 Bertani, Stephane; Fenical, William; Jensen, Paul; Le  
 Roch, Karine  
 CORPORATE SOURCE: Department of Cell Biology and Neuroscience,  
 University of California Riverside, Riverside, CA, USA  
 SOURCE: PLoS One (2008), 3(6), No pp. given  
 CODEN: POLNCL; ISSN: 1932-6203  
 URL: <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0002335>  
 PUBLISHER: Public Library of Science  
 DOCUMENT TYPE: Journal; (online computer file)  
 LANGUAGE: English  
 ABSTRACT:

Malaria continues to be a devastating parasitic disease that causes the death of 2 million individuals annually. The increase in multi-drug resistance together with the absence of an efficient vaccine hastens the need for speedy and comprehensive antimalarial drug discovery and development. Throughout history, traditional herbal remedies or natural products were a reliable source of antimalarial agents, e.g. quinine and artemisinin. Today, one emerging source of small mol. drug leads is the world's oceans. Included among the source of marine natural products are marine microorganisms such as the recently described actinomycete. Members of the genus *Salinispora* have yielded a wealth of new secondary metabolites including salinosporamide A, a mol. currently advancing through clin. trials as an anticancer agent. Because of the biol. activity of metabolites being isolated from marine microorganisms, our group became interested in exploring the potential efficacy of these compds. against the malaria parasite. We screened 80 bacterial crude exts. for their activity against malaria growth. We established that the pure compound, salinosporamide A, produced by the marine actinomycete, *Salinispora tropica*, shows strong inhibitory activity against the erythrocytic stages of the parasite cycle. Biochem. expts. support the likely inhibition of the parasite 20S proteasome. Crystal structure modeling of salinosporamide A and the parasite catalytic 20S subunit further confirm this hypothesis. Ultimately we showed that salinosporamide A protected mice against deadly malaria infection when administered at an extremely low dosage. These findings underline the potential of secondary metabolites, derived from marine microorganisms, to inhibit Plasmodium growth. More specifically, we highlight the effect of proteasome inhibitors such as salinosporamide A on in vitro and in vivo parasite development. Salinosporamide A (NPI-0052) now being advanced to phase I trials for the treatment of refractory multiple myeloma will need to be further explored to evaluate the safety profile for its use against malaria.

IT **437742-34-2P**, Salinosporamide A

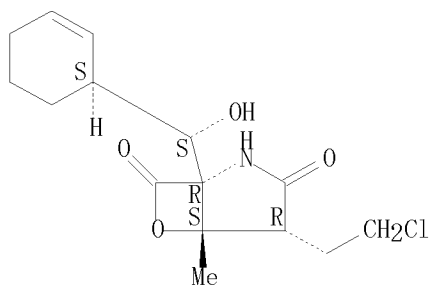
RL: PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(antimalarial salinosporamide A from *Salinispora tropica*, structure and inhibition of 20S proteasome of parasite)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 94 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2008:734102 CAPLUS  
 DOCUMENT NUMBER: 149:70422  
 TITLE: Methods and compositions VEGF antagonists for treating  
 a neoplasm  
 INVENTOR(S): Mass, Robert D.; Plowman, Greg  
 PATENT ASSIGNEE(S): Genentech, Inc., USA  
 SOURCE: PCT Int. Appl., 39pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008073509	A2	20080619	WO 2007-US68300	20070504
WO 2008073509	A3	20090108		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
AU 2007333565	A1	20080619	AU 2007-333565	20070504
CA 2670707	A1	20080619	CA 2007-2670707	20070504
KR 2009087908	A	20090818	KR 2009-7011980	20070504
EP 2099489	A2	20090916	EP 2007-761925	20070504
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR			
JP 2010512407	T	20100422	JP 2009-541425	20070504
ZA 2009003489	A	20100825	ZA 2009-3489	20070504
CN 101547705	A	20090930	CN 2007-80045106	20090605
MX 2009006202	A	20090622	MX 2009-6202	20090611
US 20100086544	A1	20100408	US 2009-518628	20091210
PRIORITY APPLN. INFO.:			US 2006-874460P	P 20061211
			WO 2007-US68300	W 20070504

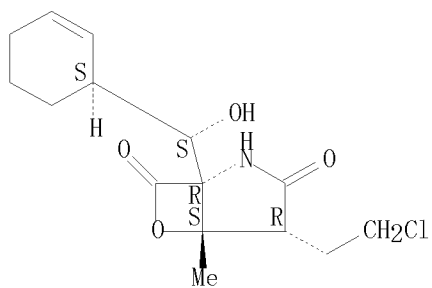
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

#### ABSTRACT:

The invention relates to compns. and methods for treating neoplasms, including refractory or relapsed neoplasms, using VEGF antagonists. Furthermore, the invention provides therapy regimens for treating those diseases.

IT **437742-34-2**, Salinosporamide A  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (methods and compns. comprising VEGF antagonists for treating a neoplasm)  
 RN **437742-34-2** CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 95 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2008:725356 CAPLUS  
DOCUMENT NUMBER: 149:70418  
TITLE: Assay for prediction of proteasome inhibitor response  
INVENTOR(S): Allen, John David; Ling, Silvia Chiu Wah  
PATENT ASSIGNEE(S): Centenary Institute of Cancer Medicine and Cell  
Biology, Australia  
SOURCE: Can. Pat. Appl., 51pp.  
CODEN: CPXXEB  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2606634	A1	20080608	CA 2007-2606634	20071012
AU 2007221966	A1	20080626	AU 2007-221966	20071012
US 20080227096	A1	20080918	US 2007-91	20071207
PRIORITY APPLN. INFO.:			AU 2006-906900	A 20061208
			AU 2007-904810	A 20070905
			AU 2007-221966	A 20071012
			US 2007-960760P	P 20071012

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

ABSTRACT:

The invention relates to a method for predicting a response to a proteasome inhibitor in the prophylaxis or treatment of a cancer in an individual. The method comprises providing a sample of cancer cells from the individual, and evaluating the level of at least one mol. in the cancer cells associated with unfolded protein response of the cancer cells, to provide test data indicative of the level of nativity of the unfolded protein response. The test data is used to predict the response of the cancer cells to the proteasome inhibitor. The evaluation of the level of the mol. can be employed to determine the treatment for the cancer.

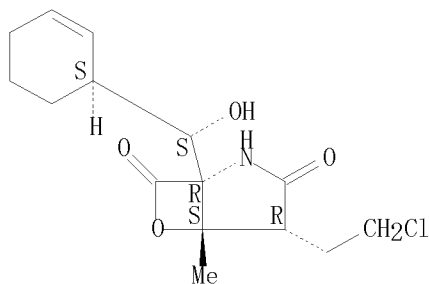
IT **437742-34-2**, NPI-0052

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(assay for prediction of proteasome inhibitor response)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

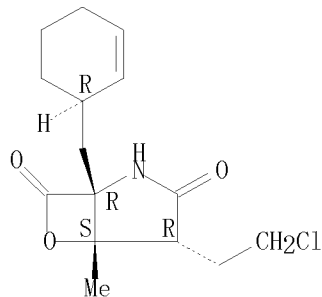


L6 ANSWER 96 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2008:665174 CAPLUS  
DOCUMENT NUMBER: 149:102768  
TITLE: Engineered Biosynthesis of Antiprotealide and Other  
Unnatural Salinosporamide Proteasome Inhibitors  
AUTHOR(S): McGlinchey, Ryan P.; Nett, Markus; Eustaquio,  
Alessandra S.; Asolkar, Ratnakar N.; Fenical, William;  
Moore, Bradley S.  
CORPORATE SOURCE: Scripps Institution of Oceanography and the Skaggs  
School of Pharmacy and Pharmaceutical Sciences,  
University of California at San Diego, La Jolla, CA,  
92093, USA  
SOURCE: Journal of the American Chemical Society (2008),  
130(25), 7822-7823  
CODEN: JACSAT; ISSN: 0002-7863  
PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
OTHER SOURCE(S): CASREACT 149:102768  
ABSTRACT:

A new shunt in the phenylalanine biosynthetic pathway to the nonproteinogenic amino acid L-3-cyclohex-2'-enylalanine was exploited in the marine bacterium *Salinispora tropica* by mutagenesis to allow for the genetic engineering of unnatural derivs. of the potent proteasome inhibitor salinosporamide A such as antiprotealide.

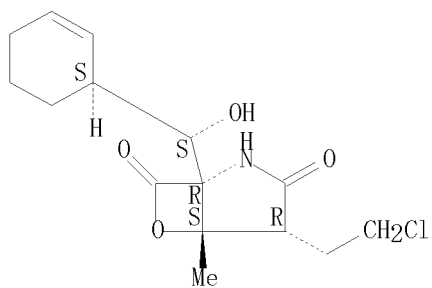
IT **932739-03-2P**, Salinosporamide J  
RL: BMF (Bioindustrial manufacture); BSU (Biological study, unclassified);  
BYP (Byproduct); PRP (Properties); PUR (Purification or recovery); BIOL  
(Biological study); PREP (Preparation)  
(engineered biosynthesis of antiprotealide and other unnatural  
salinosporamide proteasome inhibitors)  
RN 932739-03-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(1R)-2-cyclohexen-1-ylmethyl]-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

Absolute stereochemistry.



IT **437742-34-2P**, Salinosporamide A  
RL: BSU (Biological study, unclassified); BYP (Byproduct); BIOL  
(Biological study); PREP (Preparation)  
(engineered biosynthesis of antiprotealide and other unnatural  
salinosporamide proteasome inhibitors)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	23	THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (24 CITINGS)
REFERENCE COUNT:	19	THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 97 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2008:643951 CAPLUS

DOCUMENT NUMBER: 149:169872

TITLE: Mutasynthesis of fluorosalinosporamide, a potent and reversible inhibitor of the proteasome

AUTHOR(S): Eustaquio, Alessandra S.; Moore, Bradley S.

CORPORATE SOURCE: Scripps Institution of Oceanography and Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California at San Diego, La Jolla, CA, 92093-0204, USA

SOURCE: Angewandte Chemie, International Edition (2008), 47(21), 3936-3938

CODEN: ACIEF5; ISSN: 1433-7851

PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 149:169872

ABSTRACT:

Fluorine substituents give drugs with beneficial properties. By using a rational combination of genetic engineering and precursor-directed biosynthesis, fluorosalinosporamide was generated in a fermentation-based approach. A comparison of the biol. activity of three proteasome inhibitors is presented.

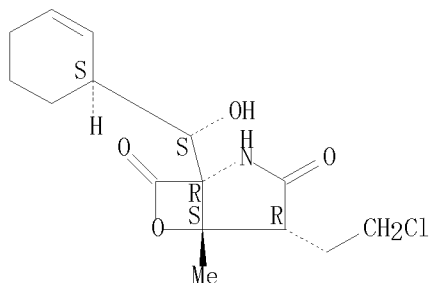
IT **437742-34-2**, Salinosporamide A

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(mutasynthesis of fluorosalinosporamide, a potent and reversible inhibitor of proteasome)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



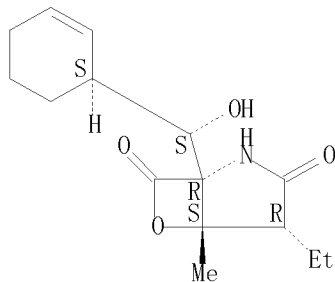
IT **863126-95-8**, Salinosporamide B **889457-14-1**

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL  
(Biological study)  
(mutasynthesis of fluorosalinosporamide, a potent and reversible inhibitor of proteasome)

RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

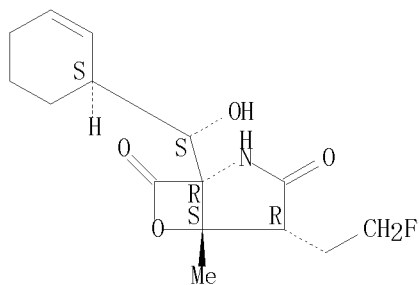
Absolute stereochemistry. Rotation (-).



RN 889457-14-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-fluoroethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT:	35	THERE ARE 35 CAPLUS RECORDS THAT CITE THIS RECORD (35 CITINGS)
REFERENCE COUNT:	30	THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 98 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2008:540825 CAPLUS

DOCUMENT NUMBER: 149:75601

TITLE: Dual targeting of the proteasome regulates survival and homing in Waldenstrom macroglobulinemia

AUTHOR(S): Rocco, Aldo M.; Leleu, Xavier; Sacco, Antonio; Jia, Xiaoying; Melhem, Molly; Moreau, Anne-Sophie; Ngo, Hai T.; Runnels, Judith; Azab, Abdelkareem; Azab, Feda; Burwick, Nicholas; Farag, Mena; Treon, Steven P.; Palladino, Michael A.; Hideshima, Teru; Chauhan, Dharminder; Anderson, Kenneth C.; Ghobrial, Irene M.

CORPORATE SOURCE: Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

SOURCE: Blood (2008), 111(9), 4752-4763  
CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: American Society of Hematology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Waldenstrom macroglobulinemia (WM) is an incurable low-grade B-cell lymphoma characterized by high protein turnover. The authors dissected the biol. role of the proteasome in WM using 2 proteasome inhibitors, NPI-0052 and bortezomib. The authors found that NPI-0052 inhibited proliferation and induced apoptosis in WM cells, and that the combination of NPI-0052 and bortezomib induced synergistic cytotoxicity in WM cells, leading to inhibition of nuclear translocation of p65NF- $\kappa$ B and synergistic induction of caspases-3, -8, and -9 and PARP cleavage. These 2 agents inhibited the canonical and non-canonical NF- $\kappa$ B pathways and acted synergistically through their differential effect on Akt activity and on chymotrypsin-like, caspase-like, and trypsin-like activities of the proteasome. The authors demonstrated that NPI-0052-induced cytotoxicity was completely abrogated in an Akt knockdown cell line, indicating that its major activity is mediated through the Akt pathway. Moreover, the authors demonstrated that NPI-0052 and bortezomib inhibited migration and adhesion in vitro and homing of WM cells in vivo, and overcame resistance induced by mesenchymal cells or by the addition of interleukin-6 in a coculture in vitro system. These studies enhance understanding of the biol. role of the proteasome pathway in WM, and provide the preclin. basis for clin. trials of combinations of proteasome inhibitors in WM.

IT 437742-34-2, NPI-0052

RL: BSU (Biological study, unclassified); DMA (Drug mechanism of action);

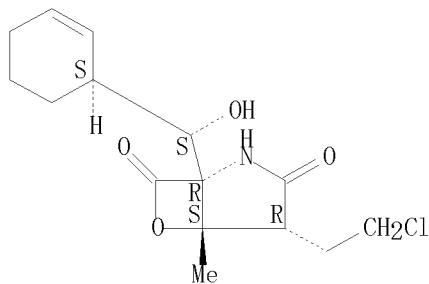
THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(cytotoxicity for Waldenstrom macroglobulinemia lymphocytes by)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



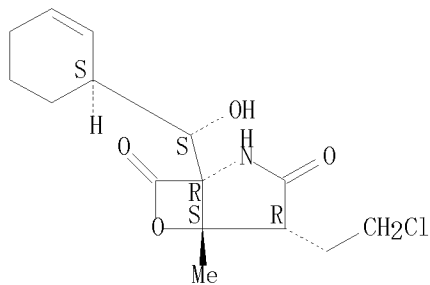
OS.CITING REF COUNT: 28 THERE ARE 28 CAPLUS RECORDS THAT CITE THIS RECORD (28 CITINGS)

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 99 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2008:535520 CAPLUS  
DOCUMENT NUMBER: 150:113802  
TITLE: The effects of proteasome inhibition on angiogenesis  
and autophagy in human prostate cancer cells  
AUTHOR(S): Zhu, Keyi  
CORPORATE SOURCE: Health Science Center, Univ. of Texas, Houston, TX,  
USA  
SOURCE: (2007) 166 pp. Avail.: UMI, Order No. DA3287365  
From: Diss. Abstr. Int., B 2008, 68(10), 6497  
DOCUMENT TYPE: Dissertation  
LANGUAGE: English  
ABSTRACT: Unavailable  
IT **437742-34-2**, NPI-0052  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(effects of proteasome inhibition on angiogenesis and autophagy in  
human prostate cancer cells)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 100 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2008:484043 CAPLUS

DOCUMENT NUMBER: 148:515495

TITLE: Inhibition of Yin Yang 1-Dependent Repressor Activity of DR5 Transcription and Expression by the Novel Proteasome Inhibitor NPI-0052 Contributes to its TRAIL-Enhanced Apoptosis in Cancer Cells

AUTHOR(S): Baritaki, Stavroula; Suzuki, Eriko; Umezawa, Kazuo; Spandidos, Demetrios A.; Berenson, James; Daniels, Tracy R.; Penichet, Manuel L.; Jazirehi, Ali R.; Palladino, Michael; Bonavida, Benjamin

CORPORATE SOURCE: Department of Microbiology, Immunology, and Molecular Genetics, University of California, Los Angeles, CA, 90095, USA

SOURCE: Journal of Immunology (2008), 180(9), 6199-6210

CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

TRAIL promotes apoptotic tumor cell death; however, TRAIL-resistant tumors need to be sensitized to reverse resistance. Proteasome inhibitors potentiate TRAIL apoptosis in vitro and in vivo and correlate with up-regulation of death receptor 5 (DR5) via an unknown mechanism. We hypothesized that the proteasome inhibitor NPI-0052 inhibits the transcription repressor Yin Yang 1 (YY1) which regulates TRAIL resistance and neg. regulates DR5 transcription. Treatment of PC-3 and Ramos cells with NPI-0052 ( $\leq 2.5$  nM) and TRAIL sensitizes the tumor cells to TRAIL-induced apoptosis. By comparison to bortezomib, a 400-fold less concentration of NPI-0052 was used. NPI-0052 up-regulated DR5 reporter activity and both surface and total DR5 protein expression. NPI-0052-induced inhibition of NF- $\kappa$ B activity was involved in TRAIL sensitization as corroborated by the use of the NF- $\kappa$ B inhibitor dehydroxymethylepoxyquinomicin. NPI-0052 inhibited YY1 promoter activity as well as both YY1 mRNA and protein expression. The direct role of NPI-0052-induced inhibition of YY1 and up-regulation of DR5 in the regulation of TRAIL sensitivity was demonstrated by the use of YY1 small interfering RNA. The NPI-0052-induced sensitization to TRAIL involved activation of the intrinsic apoptotic pathway and dysregulation of genes that regulate apoptosis. The NPI-0052 concns. used for TRAIL sensitization were not toxic to human hematopoietic stem cells. The present findings demonstrate, for the first time, the potential mechanism by which a proteasome inhibitor, like NPI-0052, inhibits the transcription repressor YY1 involved in TRAIL resistance and DR5 regulation. The findings also suggest the therapeutic application of subtoxic NPI-0052 concns. in combination with TRAIL/agonist DR4/DR5 mAbs in the treatment of TRAIL-resistant tumors.

IT 437742-34-2, NPI-0052

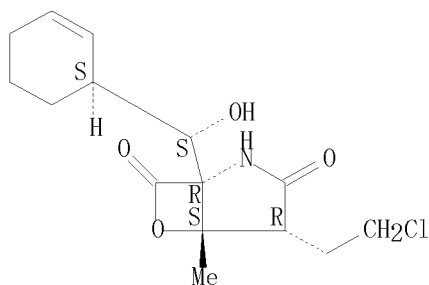
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(inhibition of yin yang 1-Dependent repressor activity of DR5 transcription and expression by novel proteasome inhibitor NPI-0052 contributes to TRAIL-Enhanced apoptosis in cancer cells)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

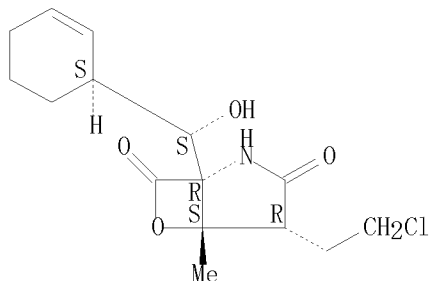


OS.CITING REF COUNT:	21	THERE ARE 21 CAPLUS RECORDS THAT CITE THIS RECORD (21 CITINGS)
REFERENCE COUNT:	59	THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 101 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2008:398987 CAPLUS  
DOCUMENT NUMBER: 148:493838  
TITLE: Blue biotechnology on the advance. New active ingredients from marine organisms  
AUTHOR(S): Wiese, Jutta; Imhoff, Johannes F.  
CORPORATE SOURCE: Kieler Wirkstoffzentrum am Leibniz Institut fuer Meereswissenschaften IFM-Geomar, Germany  
SOURCE: Bioforum (2008), 31(1), 36-37  
CODEN: BFRME3; ISSN: 0940-0079  
PUBLISHER: GIT Verlag GmbH & Co. KG  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: German  
ABSTRACT:  
A review on marine organisms as resources for the blue biotechnol. and active ingredients from marine organisms. The active ingredients conotoxin, pseudopterosine, bryostatin, ecteinascidin 743, and salinosporamide A are characterized.

IT **437742-34-2P**, Salinosporamide A  
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP (Preparation)  
(drugs from marine organisms by blue biotechnol.)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

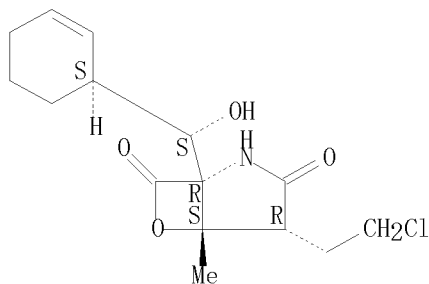
Absolute stereochemistry. Rotation (-).



L6 ANSWER 102 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2008:355282 CAPLUS  
DOCUMENT NUMBER: 149:7670  
TITLE: Defined salt formulations for the growth of  
Salinispora tropica strain NPS21184 and the production  
of salinosporamide A (NPI-0052) and related analogs  
AUTHOR(S): Tsueng, Ginger; Teisan, Sy; Lam, Kin S.  
CORPORATE SOURCE: Nereus Pharmaceuticals, Inc., San Diego, CA, 92121,  
USA  
SOURCE: Applied Microbiology and Biotechnology (2008), 78(5),  
827-832  
CODEN: AMBIDG; ISSN: 0175-7598  
PUBLISHER: Springer  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
ABSTRACT:  
Salinosporamide A (NPI-0052) is currently produced by a marine actinomycete,  
Salinispora tropica, via a saline fermentation process using a non-defined, com.  
available synthetic sea salt, Instant Ocean. In order to control the  
consistency of the production of NPI-0052 and related analogs, two chemical defined  
salt formulations were developed to replace Instant Ocean. A chemical defined  
sodium-chloride-based salt formulation with similar sodium and chloride  
contents as in Instant Ocean was found to support higher production of NPI-0052 and  
a better metabolite production profile for downstream processing than Instant  
Ocean. A chemical defined sodium-sulfate-based salt formulation with low chloride  
concentration at 17 mM was found to support a similar NPI-0052 and metabolite production  
profile as Instant Ocean. The sodium-sulfate-based formulation is a robust  
formulation for large-scale production process due to its reduced corrosiveness in  
fermentation as compared with the saline fermentation utilizing Instant Ocean or the  
sodium-chloride-based salt formulation. The production of NPI-0052 in both chemical  
defined salt formulations was successfully scaled-up to a 42-l fermentor,  
indicating that these salt formulations can be used for large-scale manufacturing  
process.

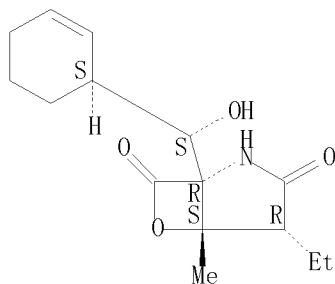
IT 437742-34-2P, Salinosporamide A 863126-95-8P,  
NPI-0047 872360-11-7P, NPI 2065  
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP  
(Preparation)  
(defined salt formulations for growth of Salinispora tropica strain  
NPS21184 and production of salinosporamide (NPI-0052) and related analogs)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

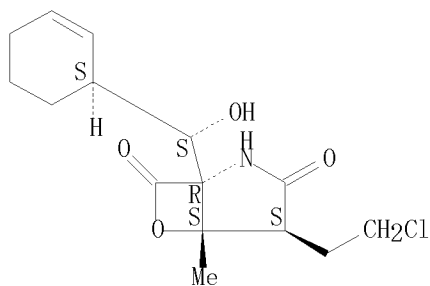
Absolute stereochemistry. Rotation (-).



RN 872360-11-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



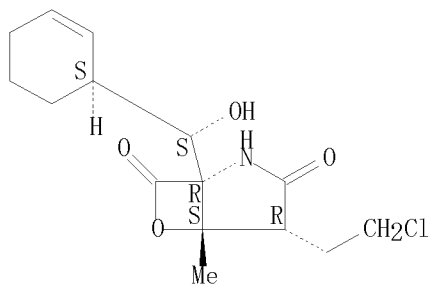
OS.CITING REF COUNT:	11	THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
REFERENCE COUNT:	24	THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 103 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2008:355272 CAPLUS  
DOCUMENT NUMBER: 148:584044  
TITLE: A low-sodium-salt formulation for the fermentation of  
salinosporamides by *Salinispora tropica* strain  
NPS21184  
AUTHOR(S): Tsueng, Ginger; Lam, Kin S.  
CORPORATE SOURCE: Nereus Pharmaceuticals, Inc., San Diego, CA, 92121,  
USA  
SOURCE: Applied Microbiology and Biotechnology (2008), 78(5),  
821-826  
CODEN: AMBIDG; ISSN: 0175-7598  
PUBLISHER: Springer  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
ABSTRACT:

In this paper, we described the development of a potassium-chloride-based-salt formulation containing low sodium concns. (5.0 to 11 mM) to support the growth of *Salinispora tropica* strain NPS21184 and its production of salinosporamide A (NPI-0052). The sodium present in the media was essentially derived from the complex nitrogen sources Hy Soy, yeast extract, and peptone used in the media. We demonstrated that good growth rate and yield of *S. tropica* strain NPS21184 were detected in both agar and liquid media containing the potassium-chloride-based-salt formulation with sodium concentration as low as 5.0 mM, significantly less than the critical seawater-growth requirement concentration of 50 mM sodium for a marine microorganism. We also observed good production of NPI-0052 (176 to 243 mg/l) by *S. tropica* strain NPS21184 grown in production media containing the potassium chloride-based-salt formulation. The production of deschloro analog, salinosporamide B (NPI-0047), was significantly lower in the low-sodium-salt-formulation medium than in the high-sodium-salt-formulation media. We demonstrated that while *S. tropica* strain NPS21184 is a novel marine actinomycete that requires high salt content for growth, it does not require sodium-chloride-based seawater-type media for growth and production of NPI-0052.

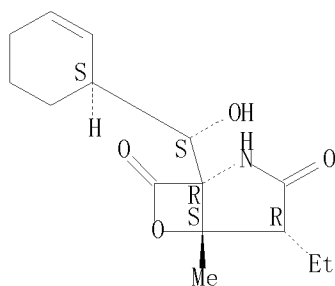
IT **437742-34-2P**, Salinosporamide A  
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP  
(Preparation)  
(low-sodium-salt formulation for fermentation of salinosporamides by  
*Salinispora tropica* strain NPS21184)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **863126-95-8P**, NPI-0047  
RL: BYP (Byproduct); PREP (Preparation)  
(low-sodium-salt formulation for fermentation of salinosporamides by  
*Salinispora tropica* strain NPS21184)  
RN 863126-95-8 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 6

THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD  
(6 CITINGS)

REFERENCE COUNT: 14

THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 104 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2008:193105 CAPLUS

DOCUMENT NUMBER: 149:44420

TITLE: Combination of proteasome inhibitors bortezomib and NPI-0052 trigger in vivo synergistic cytotoxicity in multiple myeloma

AUTHOR(S): Chauhan, Dharminder; Singh, Ajita; Brahmandam, Mohan; Podar, Klaus; Hideshima, Teru; Richardson, Paul; Munshi, Nikhil; Palladino, Michael A.; Anderson, Kenneth C.

CORPORATE SOURCE: The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Center for Myeloma Research, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

SOURCE: Blood (2008), 111(3), 1654-1664

CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: American Society of Hematology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Our recent study demonstrated that a novel proteasome inhibitor NPI-0052 triggers apoptosis in multiple myeloma (MM) cells, and importantly, that is distinct from bortezomib (Velcade) in its chemical structure, effects on proteasome activities, and mechanisms of action. Here, we demonstrate that combining NPI-0052 and bortezomib induces synergistic anti-MM activity both in vitro using MM cell lines or patient CD138+ MM cells and in vivo in a human plasmacytoma xenograft mouse model. NPI-0052 plus bortezomib-induced synergistic apoptosis is associated with: (1) activation of caspase-8, caspase-9, caspase-3, and PARP; (2) induction of endoplasmic reticulum (ER) stress response and JNK; (3) inhibition of migration of MM cells and angiogenesis; (4) suppression of chymotrypsin-like (CT-L), caspase-like (C-L), and trypsin-like (T-L) proteolytic activities; and (5) blockade of NF- $\kappa$ B signaling. Studies in a xenograft model show that low dose combination of NPI-0052 and bortezomib is well tolerated and triggers synergistic inhibition of tumor growth and CT-L, C-L, and T-L proteasome activities in tumor cells. Immunostaining of MM tumors from NPI-0052 plus bortezomib-treated mice showed growth inhibition, apoptosis, and a decrease in associated angiogenesis. Taken together, our study provides the preclin. rationale for clin. protocols evaluating bortezomib together with NPI-0052 to improve patient outcome in MM.

IT **437742-34-2**, NPI-0052

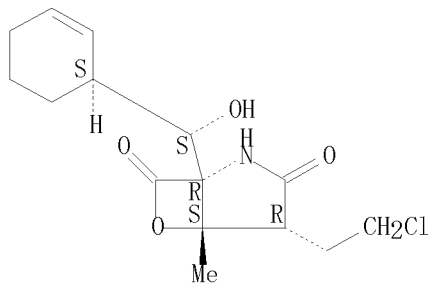
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combination of proteasome inhibitors bortezomib and NPI-0052 trigger in vivo synergistic cytotoxicity in multiple myeloma)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 73 THERE ARE 73 CAPLUS RECORDS THAT CITE THIS RECORD (73 CITINGS)

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 105 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2008:10207 CAPLUS  
DOCUMENT NUMBER: 148:120148  
TITLE: Biosynthesis of salinosporamide A and analogs and  
methods thereof  
INVENTOR(S): Moore, Bradley S.; Beer, Laura; Eustaquio, Alessandra  
S.  
PATENT ASSIGNEE(S): The University of California, USA  
SOURCE: PCT Int. Appl., 71 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008002600	A2	20080103	WO 2007-US14895	20070626
WO 2008002600	A3	20081023		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
US 20090197310	A1	20090806	US 2006-517899	20060908
US 7572606	B1	20090811		
US 20090325208	A1	20091231	US 2009-306210	20090603
PRIORITY APPLN. INFO.:			US 2006-816753P	P 20060626
			US 2005-715404P	P 20050909
			US 2006-816771P	P 20060626
			WO 2007-US14895	W 20070626

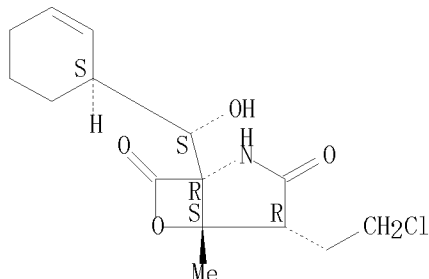
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

ABSTRACT:

The present invention relates to a salinosporamide A composition and methods of making salinosporamide A and analogs thereof. The present invention also relates to methods of identifying 20S proteasome inhibiting agents.

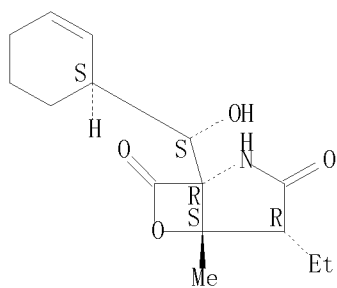
IT 437742-34-2P 863126-95-8P, Salinosporamide B  
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (biological study); PREP (Preparation)  
(biosynthesis of salinosporamide A and analogs and methods therefor)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

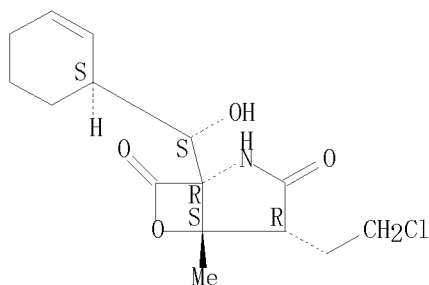
Absolute stereochemistry. Rotation (-).



L6 ANSWER 106 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:1433777 CAPLUS  
 DOCUMENT NUMBER: 148:256475  
 TITLE: Discovery and characterization of a marine bacterial SAM-dependent chlorinase  
 AUTHOR(S): Eustaquio, Alessandra S.; Pojer, Florence; Noel, Joseph P.; Moore, Bradley S.  
 CORPORATE SOURCE: Center for Marine Biotechnology and Biomedicine, Scripps Institution of Oceanography, University of California San Diego, La Jolla, CA, 92093, USA  
 SOURCE: Nature Chemical Biology (2008), 4(1), 69-74  
 CODEN: NCBABT; ISSN: 1552-4450  
 PUBLISHER: Nature Publishing Group  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 ABSTRACT: Halogen atom incorporation into a scaffold of bioactive compds. often amplifies biol. activity, as is the case for the anticancer agent salinosporamide A, a chlorinated natural product from the marine bacterium *Salinispora tropica*. Significant effort in understanding enzymic chlorination shows that oxidative routes predominate to form reactive electrophilic or radical chlorine species. Here we report the genetic, biochem. and structural characterization of the chlorinase Sall, which halogenates S-adenosyl-L-methionine with chloride to generate 5'-chloro-5'-deoxyadenosine and L-methionine in a rarely observed nucleophilic substitution strategy analogous to that of *Streptomyces cattleya* fluorinase. Further metabolic tailoring produces a halogenated polyketide synthase substrate specific for salinosporamide A biosynthesis. Sall also accepts bromide and iodide as substrates, but not fluoride. High-resolution crystal structures of Sall and active site mutants complexed with substrates and products support the SN2 nucleophilic substitution mechanism and further illuminate halide specificity in this newly discovered halogenase family.

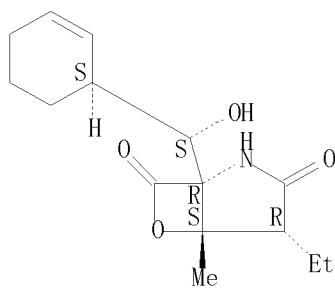
IT 437742-34-2, Salinosporamide A 863126-95-8,  
 Salinosporamide B  
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL  
 (Biological study)  
 (discovery and characterization of a marine bacterial SAM-dependent  
 chlorinase)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 34

THERE ARE 34 CAPLUS RECORDS THAT CITE THIS  
RECORD (36 CITINGS)

REFERENCE COUNT: 29

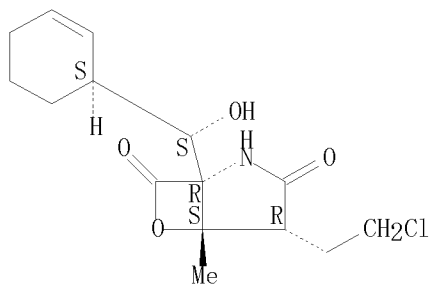
THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 107 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:1407327 CAPLUS  
DOCUMENT NUMBER: 148:528689  
TITLE: From the bench to the bedside: emerging new treatments  
in multiple myeloma  
AUTHOR(S): Mitsiades, Constantine S.; Hayden, Patrick J.;  
Anderson, Kenneth C.; Richardson, Paul G.  
CORPORATE SOURCE: Department of Medical Oncology, Dana Farber Cancer  
Institute, Harvard Medical School, Boston, MA, 02115,  
USA  
SOURCE: Best Practice & Research, Clinical Haematology (2007),  
20(4), 797-816  
CODEN: BPRCA5  
PUBLISHER: Elsevier Ltd.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

A review. Within the last decade, several novel classes of anti-myeloma therapeutics have become available. The clin. successes achieved by thalidomide, lenalidomide, and the proteasome inhibitor bortezomib, and in particular the ability of these agents to lead to major clin. responses in patients resistant to conventional or high-dose chemotherapy, have highlighted the importance of expanding further the spectrum of classes of agents utilized for the treatment of myeloma. Herein, we review the current status for the development of novel anti-myeloma agents, with emphasis on classes of therapeutics which have already translated into clin. trials or those in advanced stages of preclin. development. These include second-generation proteasome inhibitors (NPI-0052 and PR-171), heat shock protein 90 (hsp90) inhibitors, 2-methoxyestradiol, histone deacetylase (HDAC) inhibitors (e.g. SAHA and LBH589), fibroblast growth factor receptor 3 (FGF-R3) inhibitors, insulin-like growth factor 1 receptor (IGF-1R) inhibitors, mTOR inhibitors, monoclonal antibodies, and agents specifically targeting the tumor microenvironment, such as defibrotide.

IT 437742-34-2, NPI-0052  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(proteasome inhibitors like NPI-0052 and PR-171 could be used for  
treating patient with multiple myeloma)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

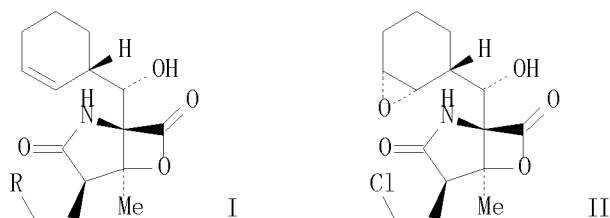


OS.CITING REF COUNT: 25 THERE ARE 25 CAPLUS RECORDS THAT CITE THIS  
RECORD (25 CITINGS)  
REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR  
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L6 ANSWER 108 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:1302848 CAPLUS  
 DOCUMENT NUMBER: 147:522016  
 TITLE: Preparation of salinosporamide A and analogous [3.2.0] bicyclic  $\beta$ -lactones for therapeutic use in the treatment of lung cancer  
 INVENTOR(S): Palladino, Michael A.  
 PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
 SOURCE: PCT Int. Appl., 248pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007130404	A1	20071115	WO 2007-US10540	20070502
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRIORITY APPLN. INFO.: US 2006-797553P P 20060503  
 OTHER SOURCE(S): CASREACT 147:522016; MARPAT 147:522016  
 GRAPHIC IMAGE:



# ABSTRACT:

Salinosporamide A I (R = Cl) and its analogs were prepared for therapeutic use in the treatment of cancer, particularly lung cancer, inflammatory conditions, and/or infectious disease. These salinosporamide analogs may be used in combination with other therapeutic agents, such as docetaxel, alimta, erlotinib, gefitinib, bevacizumab, an epidermal growth factor receptor (EGFR) inhibitor, gemcitabine, carboplatin, a histone deacetylase inhibitor, 5-fluorouracil, cisplatin, adriamycin, a topoisomerase I poison (SN-38), or a topoisomerase II poison. I (R = Cl) was prepared via a fermentation process using strain CNB476 or strain NPS21184. I (R = Cl) and related bicyclic  $\beta$ -lactones recovered from the fermentation process were subsequently converted to other  $\beta$ -lactone derivs., such as I (R = H, Br, iodo, Me) and II. The prepared  $\beta$ -lactones were tested extensively for anticancer and anti-inflammatory activity and for inhibition of Anthrax lethal toxin. Pharmaceutical compns. containing the prepared salinosporamide analogs were discussed.

IT 1044999-00-9 1057246-19-1 1057246-20-4  
1057246-22-6 1057246-23-7 1057246-24-8  
1057246-25-9 1057385-27-9

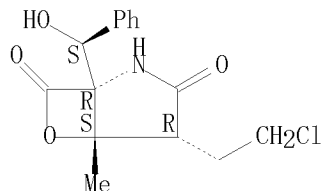
RL: PRPH (Prophetic)

(Preparation of salinosporamide A and analogous [3.2.0] bicyclic  $\beta$ -lactones for therapeutic use in the treatment of lung cancer)

RN 1044999-00-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA  
INDEX NAME)

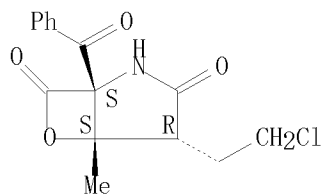
Absolute stereochemistry.



RN 1057246-19-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-benzoyl-4-(2-chloroethyl)-5-methyl-, (1S,4R,5S)- (CA INDEX NAME)

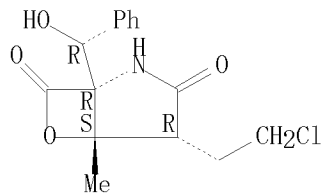
Absolute stereochemistry.



RN 1057246-20-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA  
INDEX NAME)

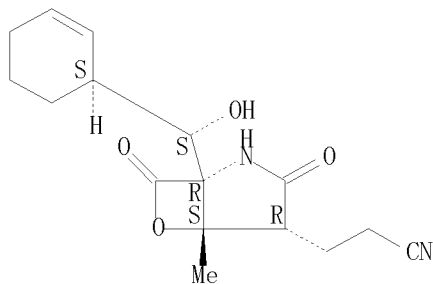
Absolute stereochemistry.



RN 1057246-22-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-4-propanenitrile,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

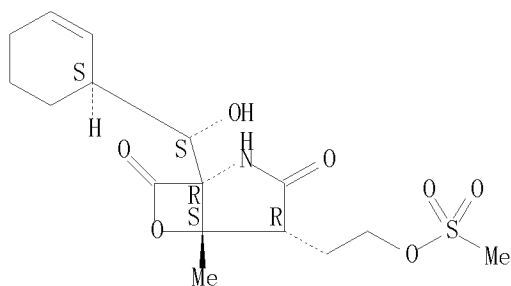


RN 1057246-23-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-  
[(methylsulfonyl)oxy]ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

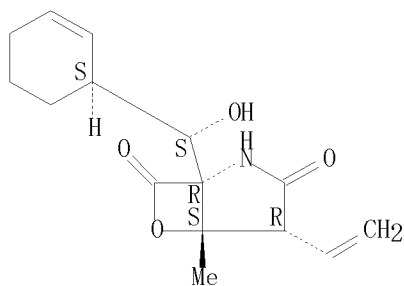
Absolute stereochemistry.





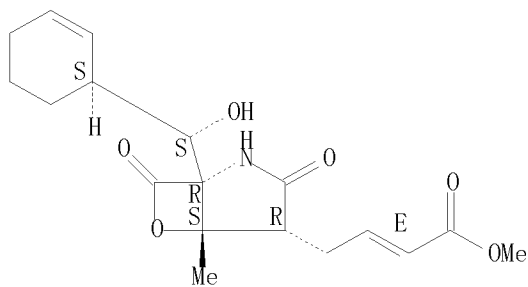
RN 1057246-24-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethenyl-5-methyl-,  
 (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



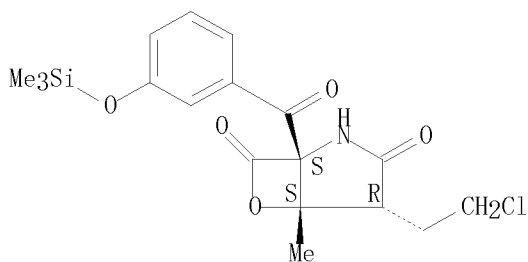
RN 1057246-25-9 CAPLUS  
 CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.  
 Double bond geometry as shown.



RN 1057385-27-9 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-5-methyl-1-[3-[(trimethylsilyl)oxy]benzoyl]-,  
 (1S, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT **823229-34-1P** **872360-17-3P**

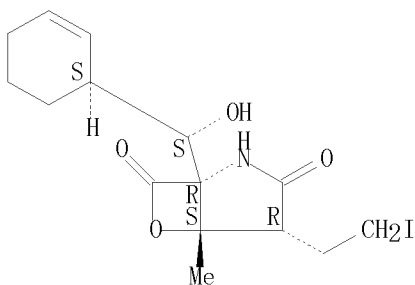
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of salinosporamide A and analogous [3.2.0] bicyclic  $\beta$ -lactones for therapeutic use in the treatment of lung cancer)

RN 823229-34-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

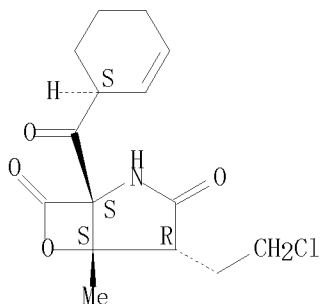
Absolute stereochemistry.



RN 872360-17-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
(1S,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

IT **437742-34-2P**, Salinosporamide A **863126-95-8P**  
**872360-15-1P**

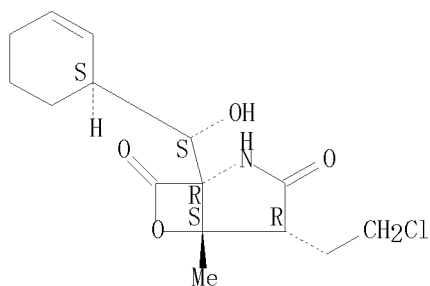
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of salinosporamide A and analogous [3.2.0] bicyclic  $\beta$ -lactones for therapeutic use in the treatment of lung cancer)

RN 437742-34-2 CAPLUS

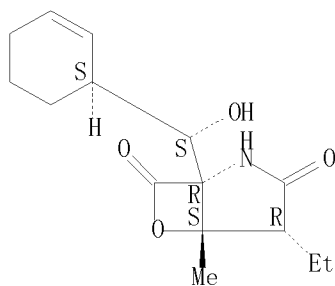
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



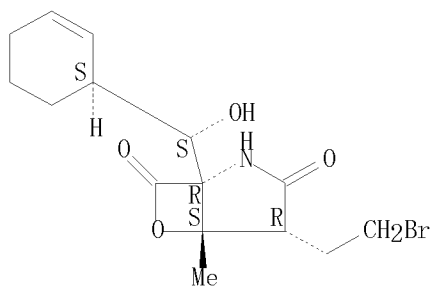
RN 863126-95-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



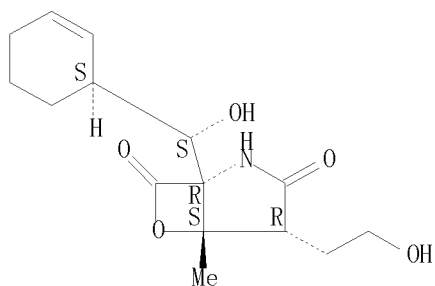
RN 872360-15-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 823229-54-5P      823229-56-7P      872360-18-4P  
872360-22-0P      872360-23-1P      872360-24-2P  
 RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN  
 (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);  
 PREP (Preparation); USES (Uses)  
 (preparation of salinosporamide A and analogous [3.2.0] bicyclic  
 β-lactones for therapeutic use in the treatment of lung cancer)  
 RN 823229-54-5 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

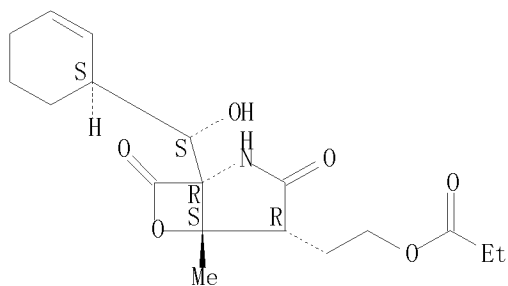
Absolute stereochemistry. Rotation (-).



RN 823229-56-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

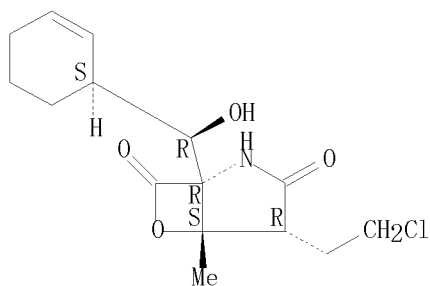
Absolute stereochemistry.



RN 872360-18-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

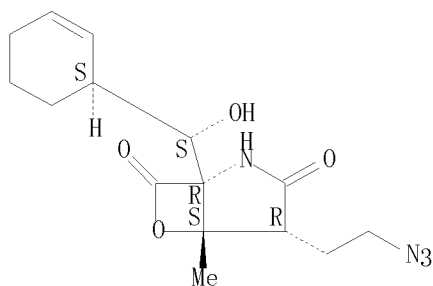
Absolute stereochemistry.



RN 872360-22-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-azidoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

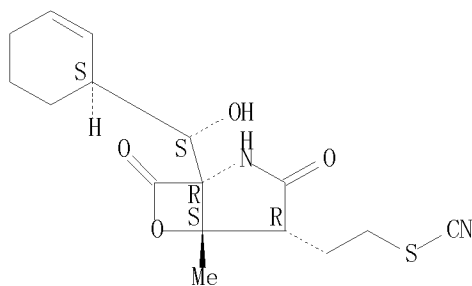
Absolute stereochemistry.



RN 872360-23-1 CAPLUS

CN Thiocyanic acid, 2-[(1R, 4R, 5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA INDEX NAME)

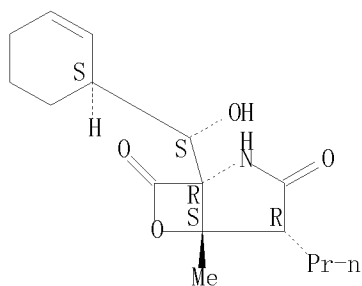
Absolute stereochemistry.



RN 872360-24-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-, (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 823229-26-1P 872360-11-7P 872360-12-8P  
872360-13-9P 872360-14-0P 872360-16-2P

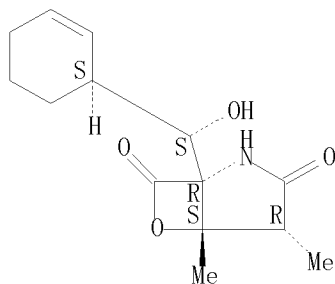
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of salinosporamide A and analogous [3.2.0] bicyclic  $\beta$ -lactones for therapeutic use in the treatment of lung cancer)

RN 823229-26-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R, 4R, 5S)- (CA INDEX NAME)

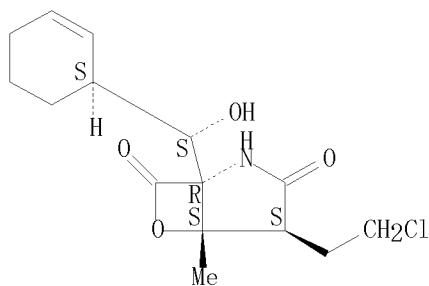
Absolute stereochemistry.



RN 872360-11-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4S,5S)- (CA INDEX NAME)

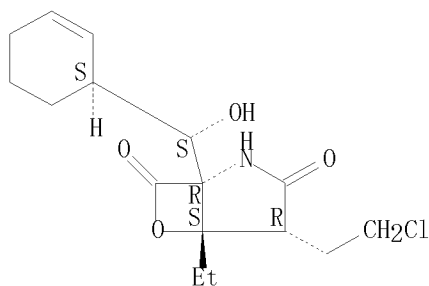
Absolute stereochemistry.



RN 872360-12-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-ethyl-,  
(1R,4R,5S)- (CA INDEX NAME)

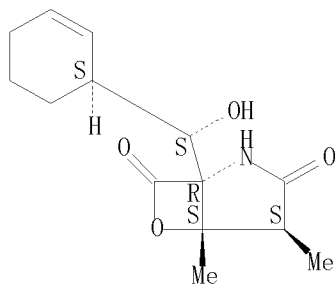
Absolute stereochemistry.



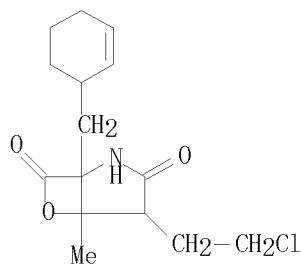
RN 872360-13-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4S,5S)-  
(CA INDEX NAME)

Absolute stereochemistry.

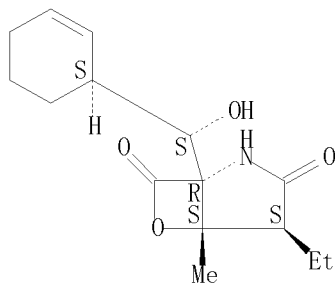


RN 872360-14-0 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-(2-cyclohexen-1-ylmethyl)-5-methyl- (CA INDEX NAME)



RN 872360-16-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4S,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD  
 (2 CITINGS)  
 REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 109 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:1204831 CAPLUS  
 DOCUMENT NUMBER: 147:467849  
 TITLE: Fermentation method  
 INVENTOR(S): Reader, Sarah Louise; Kennedy, Max James; Hinkley,  
 Simon Francis Robert; Lam, Kin Sing  
 PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
 SOURCE: PCT Int. Appl., 30pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007120801	A2	20071025	WO 2007-US9084	20070412
WO 2007120801	A3	20080214		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
PRIORITY APPLN. INFO.:			NZ 2006-546572	A 20060413
			US 2006-791625P	P 20060413

## ABSTRACT:

Methods of saline fermentation are provided. A fermenter vessel is charged with a fermentation medium having < .apprx.300 ppm Cl<sup>-</sup> ions, which is then sterilized. A sterile salt solution is added to the Cl<sup>-</sup> medium to produce a saline fermentation medium. The saline fermentation medium is then inoculated with a microorganism and the saline fermentation medium is cultured under conditions suitable for the growth of the microorganism. Finally, the medium can be harvested.

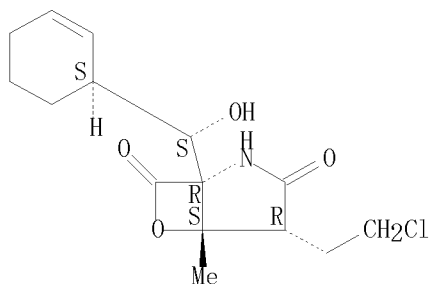
IT **437742-34-2P**, NPI-0052

RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP  
 (Preparation)  
 (fermentation in saline media)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).





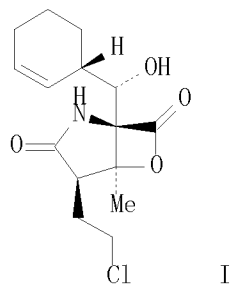
L6 ANSWER 110 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:1176380 CAPLUS  
DOCUMENT NUMBER: 147:448578  
TITLE: Total synthesis of salinosporamide A and its analogs  
with a variety of therapeutic uses in the treatment of  
cancer and other diseases  
INVENTOR(S): Ling, Taotao; Macherla, Venkata Rami Reddy; Potts,  
Barbara Christine; Manam, Rama Rao; Mearthur,  
Katherine  
PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
SOURCE: PCT Int. Appl., 308 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007117591	A2	20071018	WO 2007-US8562	20070406
WO 2007117591	A3	20080508		
WO 2007117591	A9	20081002		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
AU 2007235323	A1	20071018	AU 2007-235323	20070406
CA 2648317	A1	20071018	CA 2007-2648317	20070406
US 20070249693	A1	20071025	US 2007-697689	20070406
US 7842814	B2	20101130		
EP 2013167	A2	20090114	EP 2007-754986	20070406
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS			
JP 2009532484	T	20090910	JP 2009-504312	20070406
MX 2008012847	A	20081013	MX 2008-12847	20081006
KR 2008109071	A	20081216	KR 2008-7027066	20081104
IN 2008DN09264	A	20090327	IN 2008-DN9264	20081105
CN 101460457	A	20090617	CN 2007-80018864	20081124
PRIORITY APPLN. INFO.:			US 2006-790168P	P 20060406
			US 2006-816968P	P 20060627
			US 2006-836155P	P 20060807
			US 2006-844132P	P 20060912
			US 2007-885379P	P 20070117
			WO 2007-US8562	W 20070406

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 147:448578; MARPAT 147:448578

GRAPHIC IMAGE:



## ABSTRACT:

Methods for the preparation of salinosporamide A (I), its analogs, and its intermediates via synthetic and fermentation routes were disclosed. These compds. can be used in the fields of chemical and medicine. Salinosporamide A was assayed for inhibition of trypsin-like and chymotrypsin-like activity of the 20S proteasome.

IT **437742-34-2P**, Salinosporamide A

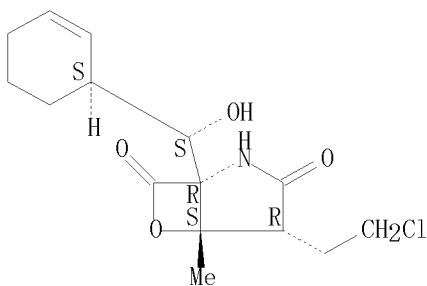
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(asym. total synthesis of and 20S proteasome activity inhibition by salinosporamide A and its analogs with therapeutic usefulness as anticancer agents)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **952512-40-2P**

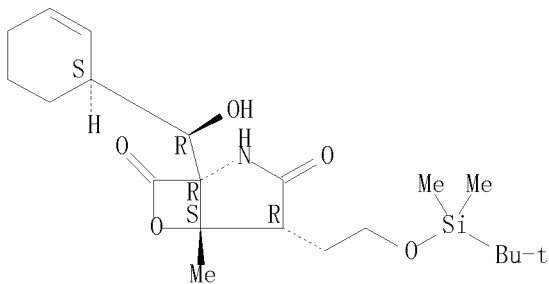
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(asym. total synthesis of and 20S proteasome activity inhibition by salinosporamide A and its analogs with therapeutic usefulness as anticancer agents)

RN 952512-40-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT **872360-17-3P** **872360-18-4P** **943542-56-1P**

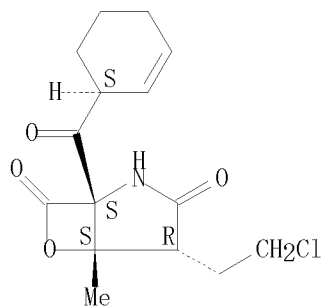
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(asym. total synthesis of and 20S proteasome activity inhibition by salinosporamide A and its analogs with therapeutic usefulness as anticancer agents)

RN 872360-17-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
(1S,4R,5S)- (CA INDEX NAME)

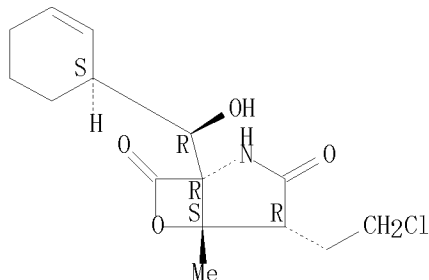
Absolute stereochemistry.



RN 872360-18-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

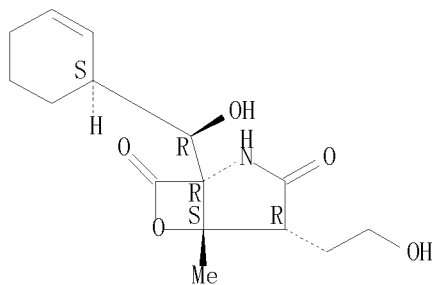
Absolute stereochemistry.



RN 943542-56-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



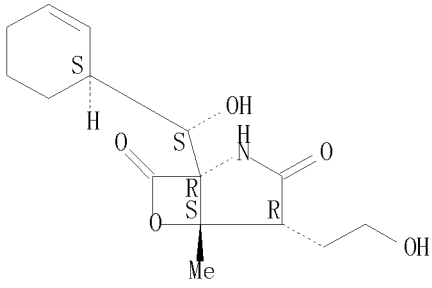
IT **823229-54-5P**

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(claimed compound; asym. total synthesis of and 20S proteasome activity inhibition by salinosporamide A and its analogs with therapeutic usefulness as anticancer agents)

RN 823229-54-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



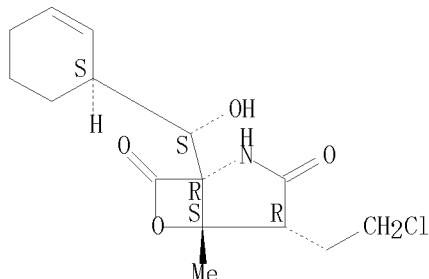
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
(1 CITINGS)

L6 ANSWER 111 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:1144323 CAPLUS  
DOCUMENT NUMBER: 147:398065  
TITLE: Salinosporamide A (NPI-0052) potentiates apoptosis, suppresses osteoclastogenesis, and inhibits invasion through down-modulation of NF- $\kappa$ B-regulated gene products  
AUTHOR(S): Ahn, Kwang Seok; Sethi, Gautam; Chao, Ta-Hsiang; Neuteboom, Saskia T. C.; Chaturvedi, Madan M.; Palladino, Michael A.; Younes, Anas; Aggarwal, Bharat B.  
CORPORATE SOURCE: Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, USA  
SOURCE: Blood (2007), 110(7), 2286-2295  
CODEN: BLOOAW; ISSN: 0006-4971  
PUBLISHER: American Society of Hematology  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
ABSTRACT:

Salinosporamide A (also called NPI-0052), recently identified from the marine bacterium *Salinispora tropica*, is a potent inhibitor of 20S proteasome and exhibits therapeutic potential against a wide variety of tumors through a poorly understood mechanism. Here we demonstrate that salinosporamide A potentiated the apoptosis induced by tumor necrosis factor  $\alpha$  (TNF), bortezomib, and thalidomide, and this correlated with down-regulation of gene products that mediate cell proliferation (cyclin D1, cyclooxygenase-2 [COX-2], and c-Myc), cell survival (Bcl-2, Bcl-xL, cFLIP, TRAF1, IAP1, IAP2, and survivin), invasion (matrix metalloproteinase-9 [MMP-9] and ICAM-1), and angiogenesis (vascular endothelial growth factor [VEGF]). Salinosporamide A also suppressed TNF-induced tumor cell invasion and receptor activator of nuclear factor  $\kappa$ B ligand (RANKL)-induced osteoclastogenesis. We also found that it suppressed both constitutive and inducible NF- $\kappa$ B activation. Compared with bortezomib, MG-132, N-acetyl-leucyl-leucyl-norleucinal (ALLN), and lactacystin, salinosporamide A was found to be the most potent suppressor of NF- $\kappa$ B activation. Further studies showed that salinosporamide A inhibited TNF-induced inhibitory subunit of NF- $\kappa$ B  $\alpha$  (I $\kappa$ B $\alpha$ ) degradation, nuclear translocation of p65, and NF- $\kappa$ B-dependent reporter gene expression but had no effect on I $\kappa$ B $\alpha$  kinase activation, I $\kappa$ B $\alpha$  phosphorylation, or I $\kappa$ B $\alpha$  ubiquitination. Thus, overall, our results indicate that salinosporamide A enhances apoptosis, suppresses osteoclastogenesis, and inhibits invasion through suppression of the NF- $\kappa$ B pathway.

IT 437742-34-2, Salinosporamide A  
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(salinosporamide A inhibits NF- $\kappa$ B-regulated gene products)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



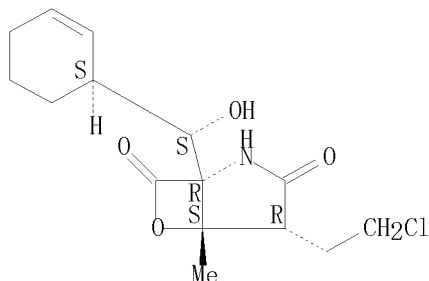
OS.CITING REF COUNT: 32 THERE ARE 32 CAPLUS RECORDS THAT CITE THIS RECORD (32 CITINGS)  
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 112 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:938689 CAPLUS  
DOCUMENT NUMBER: 147:425567  
TITLE: Stabilization effect of resin on the production of  
potent proteasome inhibitor NPI-0052 during submerged  
fermentation of *Salinispora tropica*  
AUTHOR(S): Tsueng, Ginger; Lam, Kin S.  
CORPORATE SOURCE: Nereus Pharmaceuticals, Inc., San Diego, CA, 92121,  
USA  
SOURCE: Journal of Antibiotics (2007), 60(7), 469-472  
CODEN: JANTAJ; ISSN: 0021-8820  
PUBLISHER: Japan Antibiotics Research Association  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
ABSTRACT:  
Addition of acrylic resin Amberlite XAD-7 during the fermentation of *Salinispora tropica* significantly enhanced the production of NPI-0052 by 69 fold. Examination of the time course of resin addition to the *Salinispora tropica* fermentation demonstrated that the increase in the production of NPI-052 is due to the stabilization effect by resin but not the removal of an end product feedback repression. Delay in resin addition to the fermentation led to decreases in the production of NPI-0052 to the amts. that are synthesized prior to the resin addition

IT 437742-34-2P, NPI-0052  
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP  
(Preparation)  
(ion exchangers stabilize the production of salinosporamide A during  
submerged fermentation of *Salinispora tropica*)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



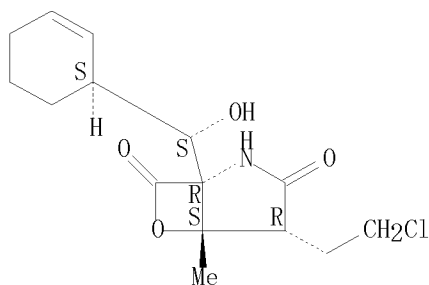
OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS  
RECORD (11 CITINGS)  
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 113 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:870312 CAPLUS  
 DOCUMENT NUMBER: 147:371363  
 TITLE: A mechanistic and kinetic study of the  $\beta$ -lactone hydrolysis of salinosporamide A (NPI-0052), a novel proteasome inhibitor  
 AUTHOR(S): Denora, Nunzio; Potts, Barbara C. M.; Stella, Valentino J.  
 CORPORATE SOURCE: Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, KS, 66047, USA  
 SOURCE: Journal of Pharmaceutical Sciences (2007), 96(8), 2037-2047  
 CODEN: JPMSAE; ISSN: 0022-3549  
 PUBLISHER: Wiley-Liss, Inc.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 ABSTRACT:

The aim of the present study was to investigate the mechanism of aqueous degradation of Salinosporamide A (NPI-0052) (I), a potent proteasome inhibitor that is currently in Phase I clin. trials for the treatment of cancer and is characterized by a unique  $\beta$ -lactone- $\gamma$ -lactam bicyclic ring structure. The degradation of I was monitored by HPLC and by both low- and high-resolution mass spectral analyses. Apparent first-order rate consts. for the degradation at 25° were determined in aqueous buffer solns. (ionic strength 0.15M adjusted with NaCl) at various pH values in the range of 1-9. Degradation kinetics in water and in deuterium oxide were compared as a mechanistic probe. The studies were performed at pH 4.5 at 25°. To further confirm the reaction mechanism, the degradation was also performed in 18O-enriched water and the degradation products subjected to HPLC separation prior to mass spectral anal. Solubility and stability in (SBE)7m- $\beta$ -cyclodextrin (Captisol) solns. were also determined. The hydrolytic degradation of I, followed by both HPLC and LC/MS, showed that the drug in aqueous solns. gives a species with a mol. ion consistent with the  $\beta$ -lactone hydrolysis product (NPI-2052). This initial degradant further rearranges to a cyclic ether (NPI-2055) via an intramol. nucleophilic displacement reaction. The kinetic results showed that the degradation of I was moderately buffer catalyzed (general base) and the rate consts. were pH independent in the range of 1-5 and base dependent above pH 6.5. No acid catalysis was observed. The kinetic deuterium solvent isotope effect (KSIE) was 3.1 (kH/kD) and a linear proton inventory plot showed that the rate-determining step involved only a single proton transfer. This suggested that a neighboring hydroxyl group (as opposed to a second water mol.) facilitated water attack at pD 4.5. Mass spectral anal. from the 18O-labeling studies proved that the mechanism involves acyl-oxygen bond cleavage and not a carbonium ion mechanism. I is unstable in water ( $t_{90\%} \leq 33$  min at pH <5) and degrades via  $\beta$ -lactone hydrolysis involving a normal ester hydrolysis mechanism (addition-elimination) resulting in acyl-oxygen bond cleavage. Captisol solubilized and stabilized I in aqueous solns.

IT **437742-34-2**, Salinosporamide A  
 RL: PRP (Properties); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)  
 (mechanistic and kinetic study of  $\beta$ -lactone hydrolysis of salinosporamide A)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

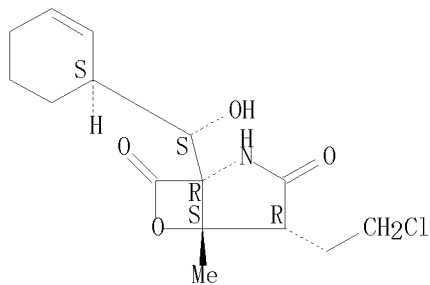




OS.CITING REF COUNT:	13	THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)
REFERENCE COUNT:	22	THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 114 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:803496 CAPLUS  
DOCUMENT NUMBER: 147:184295  
TITLE: Studies on the biosynthesis and isolation of the  
biosynthetic gene cluster for the salinosporamides of  
the marine bacterium *Salinispora tropica*  
AUTHOR(S): Beer, Laura Lynn  
CORPORATE SOURCE: Univ. of Arizona, Tucson, AZ, USA  
SOURCE: (2006) 245 pp. Avail.: UMI, Order No. DA3239540  
From: Diss. Abstr. Int., B 2007, 67(10), 5681  
DOCUMENT TYPE: Dissertation  
LANGUAGE: English  
ABSTRACT: Unavailable  
IT 437742-34-2, *Salinisporamide A*  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(studies on the biosynthesis and isolation of the biosynthetic gene  
cluster for the salinosporamides of the marine bacterium *Salinispora*  
*tropica*)  
RN 437742-34-2 CAPLUS  
CN 6-0xa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 115 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:742137 CAPLUS  
DOCUMENT NUMBER: 147:268331  
TITLE: NPI-0052, a novel proteasome inhibitor, induces  
caspase-8 and ROS-dependent apoptosis alone and in  
combination with HDAC inhibitors in leukemia cells  
AUTHOR(S): Miller, Claudia P.; Ban, Kechen; Dujka, Melanie E.;  
McConkey, David J.; Munsell, Mark; Palladino, Michael;  
Chandra, Joya  
CORPORATE SOURCE: Department of Pediatrics Research, M. D. Anderson  
Cancer Center, Houston, TX, USA  
SOURCE: Blood (2007), 110(1), 267-277  
CODEN: BLOOAW; ISSN: 0006-4971  
PUBLISHER: American Society of Hematology  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
ABSTRACT:

The proteasome has been successfully targeted for the treatment of multiple myeloma and mantle cell lymphoma; however, in other hematol. malignancies, bortezomib has been less effective as a single agent. Here, we describe effects of NPI-0052, a novel proteasome inhibitor, in leukemia model systems. In cell lines, NPI-0052 inhibits all 3 proteolytic activities associated with the proteasome: chymotrypsin-, trypsin-, and caspase-like. NPI-0052 also induces DNA fragmentation in leukemia lines and in mononuclear cells from a Ph + acute lymphoblastic leukemia (ALL) patient. Caspase-3 activation by NPI-0052 was seen in wild-type Jurkat cells, but was significantly lessened in Fas-associated death domain (FADD)-deficient or caspase-8-deficient counterparts. NPI-0052-induced apoptosis was further probed using caspase-8 inhibitors, which were more protective than caspase-9 inhibitors. N-acetyl cysteine (NAC) also conferred protection against NPI-0052-induced apoptosis, indicating a role for oxidative stress by NPI-0052. In support of the drug's in vitro activities, biweekly treatment with NPI-0052 lessened total white blood cell (WBC) burden over 35 days in leukemic mice. Interestingly, combining NPI-0052 with either MS-275 or valproic acid (VPA) induced greater levels of cell death than the combination of bortezomib with these histone deacetylase inhibitors (HDACI). These effects of NPI-0052, alone and in combination with HDACI, warrant further testing to determine the compound's clin. efficacy in leukemia.

IT 437742-34-2, NPI0052

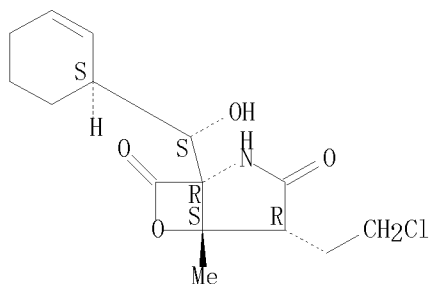
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(NPI-0052, proteasome inhibitor, induces caspase-8 and ROS-dependent apoptosis alone and in combination with HDAC inhibitors in leukemia cells)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 65 THERE ARE 65 CAPLUS RECORDS THAT CITE THIS  
RECORD (66 CITINGS)  
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 116 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:647473 CAPLUS  
DOCUMENT NUMBER: 147:64514  
TITLE: Inhibitors of histone deacetylase for the treatment of disease  
INVENTOR(S): Bonnefous, Celine; Payne, Joseph E.; Smith, Nicholas D.; Hoffman, Timothy Z.; Sertic, Michael; Wash, Paul L.; Malecha, James W.  
PATENT ASSIGNEE(S): Kalypsys, Inc., USA  
SOURCE: PCT Int. Appl., 60pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 3  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007067993	A1	20070614	WO 2006-US61820	20061208
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
PRIORITY APPLN. INFO.:			US 2005-748822P	P 20051209
			US 2005-748823P	P 20051209
			US 2006-784644P	P 20060320
			US 2006-802823P	P 20060522

OTHER SOURCE(S): MARPAT 147:64514

ABSTRACT:

Disclosed herein are compds. and methods used for treating disease states including, but not limited to cancers, autoimmune diseases, tissue damage, central nervous system disorders, neurodegenerative disorders, fibrosis, bone disorders, polyglutamine-repeat disorders, anemias, thalassemias, inflammatory conditions, cardiovascular conditions, and disorders in which angiogenesis play a role in pathogenesis. In addition, methods of modulating the activity of histone deacetylase (HDAC) are also disclosed.

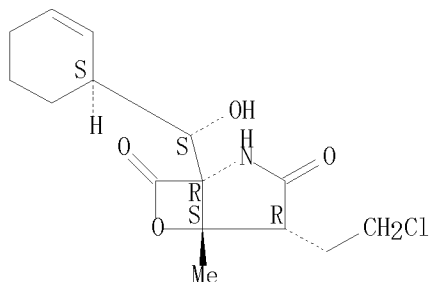
IT 437742-34-2, NPI0052

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(histone deacetylase inhibitors)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)  
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

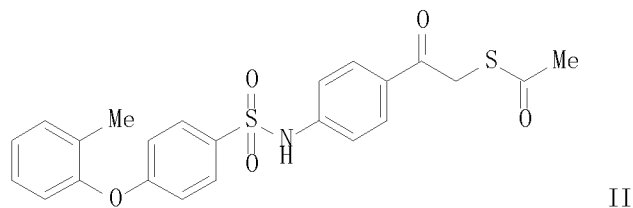
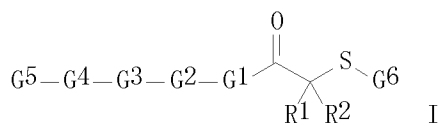
L6 ANSWER 117 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:647471 CAPLUS  
 DOCUMENT NUMBER: 147:72539  
 TITLE: Preparation of N-phenyl/pyridyl benzenesulfonamides as histone deacetylase inhibitors for the treatment of disease  
 INVENTOR(S): Smith, Nicholas D.; Bonnefous, Celine; Payne, Joseph E.; Hoffman, Timothy Z.; Wash, Paul L.; Hassig, Christian A.; Scranton, Shawn A.  
 PATENT ASSIGNEE(S): Kalypsys, Inc., USA  
 SOURCE: PCT Int. Appl., 62pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007067994	A1	20070614	WO 2006-US61821	20061208
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AR 58296	A1	20080130	AR 2006-105429	20061207
US 20070135431	A1	20070614	US 2006-608726	20061208
PRIORITY APPLN. INFO.:			US 2005-748823P	P 20051209
			US 2006-802823P	P 20060522

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 147:72539; MARPAT 147:72539

GRAPHIC IMAGE:



#### ABSTRACT:

The title compds. I [G1 = (un)substituted 5-6 membered (hetero)aryl; G2 = N-sulfonamide moiety; G3 = (un)substituted Ph, 5-6 membered (hetero)aryl; R1, R2 = H, alkyl, halo, perhaloalkyl; or R1 and R2 taken together may form an optionally substituted (hetero)cycloalkyl; G4 = (CR<sup>5</sup>R<sup>6</sup>)<sub>m</sub>, SO<sub>2</sub>, etc.; R<sup>5</sup>, R<sup>6</sup> = H, alkyl, alkoxy, etc.; m = 1-6; G5 = (un)substituted (hetero)aryl, (hetero)cycloalkyl, etc.; G6 = H, acyl, aryl, etc.], useful for treating disease states including, but not limited to cancers, autoimmune diseases, tissue damage, central nervous system disorders, neurodegenerative disorders, fibrosis, bone disorders, polyglutamine-repeat disorders, anemias, thalassemias, inflammatory conditions, cardiovascular conditions, and disorders in which angiogenesis play a role in pathogenesis, were prepared E.g., a multi-step synthesis of II, starting from 4-(o-tolyloxy)benzenesulfonyl

chloride and 1-(4-aminophenyl)ethanone, was given. II showed IC<sub>50</sub> of  $\leq 1$   $\mu\text{M}$  against HDAC (in vitro). Pharmaceutical composition comprising the compound I is claimed. In addition, methods of modulating the activity of histone deacetylase (HDAC) are also disclosed.

IT 437742-34-2, NPI0052

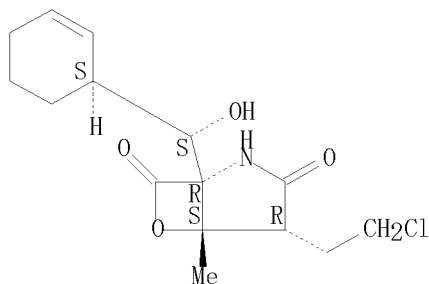
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(codrug; preparation of N-phenyl/pyridyl benzenesulfonamides as histone deacetylase inhibitors useful in treatment and prevention of diseases)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	6	THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT:	4	THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 118 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:647470 CAPLUS  
 DOCUMENT NUMBER: 147:64513  
 TITLE: Inhibitors of histone deacetylase for the treatment of disease  
 INVENTOR(S): Payne, Joseph E.; Smith, Nicholas D.; Scranton, Shawn A.; Hassig, Christian A.  
 PATENT ASSIGNEE(S): Kalypsys, Inc., USA  
 SOURCE: PCT Int. Appl., 43 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007067995	A2	20070614	WO 2006-US61823	20061208
WO 2007067995	A3	20071122		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
AR 59952	A1	20080514	AR 2006-105428	20061207
US 20070135438	A1	20070614	US 2006-608736	20061208
EP 1959967	A2	20080827	EP 2006-840175	20061208
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR			
IN 2008KN02458	A	20090417	IN 2008-KN2458	20080618
PRIORITY APPLN. INFO.:			US 2005-748822P	P 20051209
			US 2006-784644P	P 20060320
			US 2006-802829P	P 20060522
			WO 2006-US61823	W 20061208

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 147:64513

#### ABSTRACT:

Disclosed herein are carbonyl compds. of having the structural formula (I) or a pharmaceutically acceptable salt, ester, or prodrug thereof, Methods and compns. are disclosed for treating disease states including, but not limited to cancers, autoimmune diseases, tissue damage, central nervous system disorders, neurodegenerative disorders, fibrosis, bone disorders, polyglutamine-repeat disorders, anemias, thalassemias, inflammatory conditions, cardiovascular conditions, and disorders in which angiogenesis play a role in pathogenesis, using the compds. of the invention. In addition, methods of modulating the activity of histone deacetylase (HDAC) are also disclosed.

IT 437742-34-2, NPI0052

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

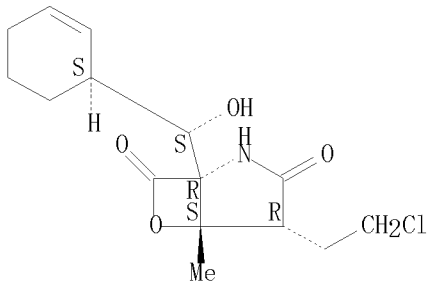
(inhibitors of histone deacetylase for treatment of disease)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).





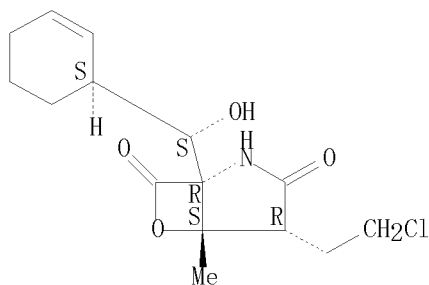
OS.CITING REF COUNT: 3

THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD  
(3 CITINGS)

L6 ANSWER 119 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:646941 CAPLUS  
 DOCUMENT NUMBER: 147:321328  
 TITLE: Unique butyric acid incorporation patterns for salinosporamides A and B reveal distinct biosynthetic origins  
 AUTHOR(S): Tsueng, Ginger; McArthur, Katherine A.; Potts, Barbara C. M.; Lam, Kin S.  
 CORPORATE SOURCE: Nereus Pharmaceuticals, San Diego, CA, 92121, USA  
 SOURCE: Applied Microbiology and Biotechnology (2007), 75(5), 999-1005  
 CODEN: AMBIDG; ISSN: 0175-7598  
 PUBLISHER: Springer  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 ABSTRACT: Feeding sodium butyrate (0.25-1 mg/mL) to cultures of *Salinispora tropica* NPS21184 enhanced the production of salinosporamide B (NPI-0047) by 319% while inhibiting the production of salinosporamide A (NPI-0052) by 26%. Liquid chromatog. mass spectrometry anal. of the crude extract from the strain NPS21184 fed with 0.5 mg/mL sodium [U-13C4]butyrate indicated that butyrate was incorporated as a contiguous four-carbon unit into NPI-0047 but not into NPI-0052. NMR anal. of NPI-0047 and NPI-0052 purified from the sodium [U-13C4]butyrate-supplemented culture extract confirmed this incorporation pattern. The above finding is the first direct evidence to demonstrate that the biosynthesis of NPI-0047 is different from NPI-0052, and NPI-0047 is not a precursor of NPI-0052.

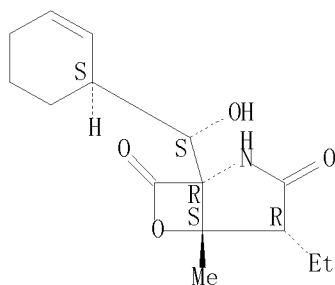
IT 437742-34-2P, Salinosporamide A 863126-95-8P,  
 Salinosporamide B  
 RL: BMF (Bioindustrial manufacture); BSU (Biological study, unclassified);  
 BIOL (Biological study); PREP (Preparation)  
 (unique butyric acid incorporation patterns for salinosporamides and B  
 reveal distinct biosynthetic origins)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	8	THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT:	15	THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 120 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:538243 CAPLUS  
 DOCUMENT NUMBER: 146:493522  
 TITLE: Methods of sensitizing cancer to therapy-induced  
 cytotoxicity  
 INVENTOR(S): Bonavida, Benjamin; Palladino, Michael  
 PATENT ASSIGNEE(S): The Regents of the University of California, USA;  
 Nereus Pharmaceuticals  
 SOURCE: PCT Int. Appl., 77pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007056335	A2	20070518	WO 2006-US43277	20061106
WO 2007056335	A3	20080117		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
AU 2006311734	A1	20070518	AU 2006-311734	20061106
CA 2628110	A1	20070518	CA 2006-2628110	20061106
EP 1951226	A2	20080806	EP 2006-837019	20061106
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS			
US 20090148445	A1	20090611	US 2009-282343	20090219
PRIORITY APPLN. INFO.:			US 2005-733965P	P 20051104
			US 2006-840811P	P 20060828
			WO 2006-US43277	W 20061106

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 146:493522

#### ABSTRACT:

The present application demonstrates that Salinosporamide A can be used to sensitize cancer cells to cancer therapy. Furthermore, the present application demonstrates that Salinosporamide A acts as a therapeutic agent to kill or inhibit cancer cells after sensitization of the cells by an antibody or other chemosensitizing reagents. The cancer cells can be either therapy-sensitive or therapy-resistant. The present application further demonstrates that Salinosporamide A induces the expression of Raf kinase inhibitor protein (RKIP) and PTEN, tumor suppressor proteins, and inhibits the expression of YY1, a transcriptional regulator protein overexpressed in cancer cells and also inhibits the growth factor pleiotrophin (PTN).

IT 437742-34-2, Salinosporamide A 437742-34-2D,

Salinosporamide A, stereoisomers

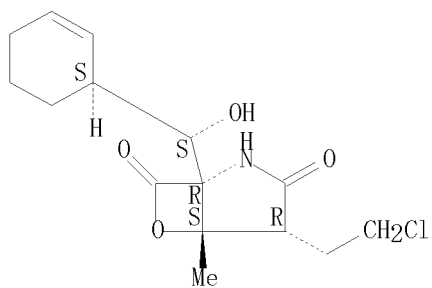
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(methods of sensitizing cancer to therapy-induced cytotoxicity using Salinosporamide A in relation to induction of apoptosis and mechanism)

RN 437742-34-2 CAPLUS

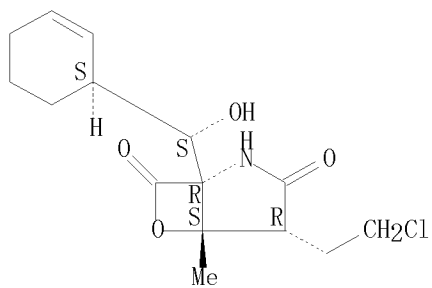
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

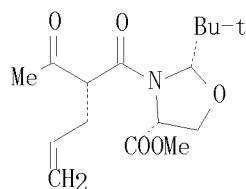
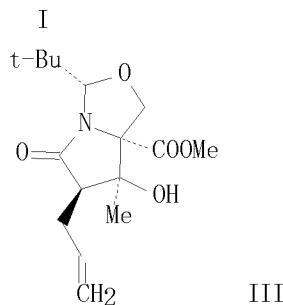
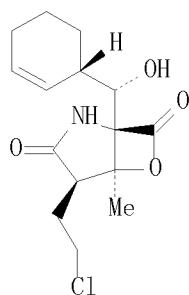


RN 437742-34-2 CAPLUS  
CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L6 ANSWER 121 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:514103 CAPLUS  
 DOCUMENT NUMBER: 147:166081  
 TITLE: Enantioselective Total Synthesis of  
 (-)-Salinosporamide A (NPI-0052)  
 AUTHOR(S): Ling, Taotao; Macherla, Venkat R.; Manam, Rama Rao;  
 McArthur, Katherine A.; Potts, Barbara C. M.  
 CORPORATE SOURCE: Nereus Pharmaceuticals, Inc., San Diego, CA, 92121,  
 USA  
 SOURCE: Organic Letters (2007), 9(12), 2289-2292  
 CODEN: ORLEF7; ISSN: 1523-7060  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 147:166081  
 GRAPHIC IMAGE:

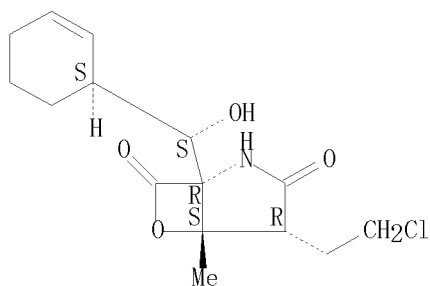


# ABSTRACT:

A novel enantioselective total synthesis of 20S proteasome inhibitor salinosporamide A (NPI-0052; I) is presented. Key features include intramol. aldol cyclization of II to simultaneously generate the three chiral centers of advanced intermediate III, cyclohexene ring addition using B-2-cyclohexen-1-yl-9-BBN, and inversion of the C-5 stereocenter by oxidation followed by enantioselective enzymic reduction

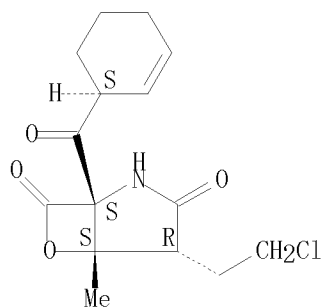
IT **437742-34-2P**, (-)-Salinosporamide A  
 RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (total synthesis of (-)-salinosporamide A involves an intramol. aldol cyclization to simultaneously generate three chiral centers of an advanced intermediate)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



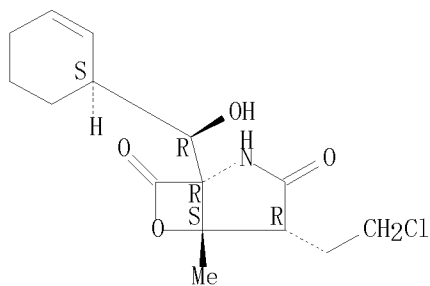
IT 872360-17-3P 872360-18-4P 943542-56-1P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (total synthesis of (-)-salinosporamide A involves an intramol. aldol  
 cyclization to simultaneously generate three chiral centers of an  
 advanced intermediate)  
 RN 872360-17-3 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
 (1S, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



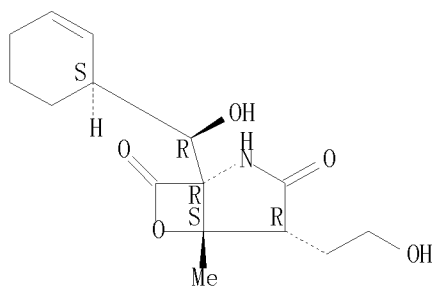
RN 872360-18-4 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 943542-56-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
 (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT:	33	THERE ARE 33 CAPLUS RECORDS THAT CITE THIS RECORD (34 CITINGS)
REFERENCE COUNT:	19	THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

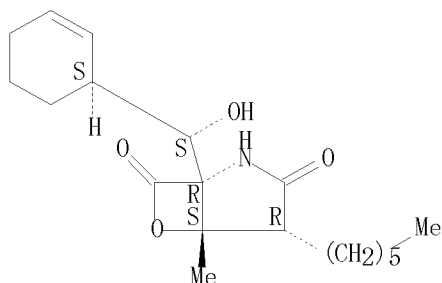


L6 ANSWER 122 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:488614 CAPLUS  
 DOCUMENT NUMBER: 147:95453  
 TITLE: Concise Total Synthesis of ( $\pm$ )-SalinosporamideA,  
 ( $\pm$ )-CinnabaramideA, and Derivatives via a  
 Bis-cyclization Process: Implications for a  
 Biosynthetic Pathway?  
 AUTHOR(S): Ma, Gil; Nguyen, Henry; Romo, Daniel  
 CORPORATE SOURCE: Department of Chemistry, Texas A & M University,  
 College Station, TX, 77842-3012, USA  
 SOURCE: Organic Letters (2007), 9(11), 2143-2146  
 CODEN: ORLEF7; ISSN: 1523-7060  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 147:95453  
 ABSTRACT:

4-Alkylidene- $\beta$ -lactones (hetero ketene dimers) and  $\alpha$ -amino acids are useful precursors for total syntheses of the  $\beta$ -lactone-containing proteasome inhibitors salinosporamide A, cinnabaramide A, and derivs. A key step is a nucleophile-promoted, bis-cyclization of keto acids that simultaneously generates the  $\gamma$ -lactam and  $\beta$ -lactone of these natural products. This reaction sequence may have implications for the biosynthesis of these natural products.

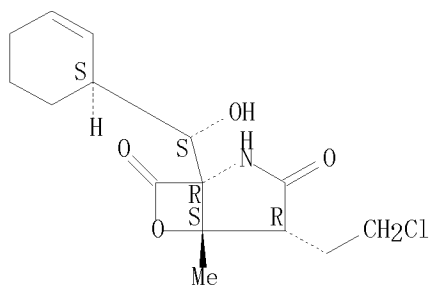
IT **942516-89-4P**, ( $\pm$ )-CinnabaramideA  
 RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)  
 (mol. and crystal structure; total synthesis of ( $\pm$ )-salinosporamide  
 A, ( $\pm$ )-cinnabaramideA, and derivs. via a bis-cyclization process)  
 RN 942516-89-4 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-,  
 (1S,4S,5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



IT **909569-43-3P**, ( $\pm$ )-SalinosporamideA  
 RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)  
 (mol. crystal structure; total synthesis of ( $\pm$ )-salinosporamideA,  
 ( $\pm$ )-cinnabaramideA, and derivs. via a bis-cyclization process)  
 RN 909569-43-3 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1S,4S,5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



IT 942517-04-6P 942517-09-1P

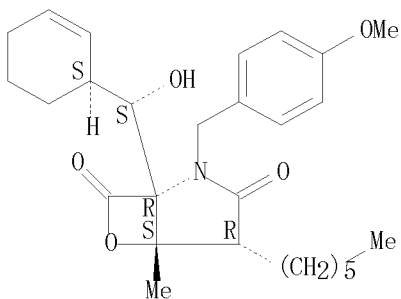
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of (±)-salinosporamideA, (±)-cinnabaramideA, and derivs. via a bis-cyclization process)

RN 942517-04-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-2-[(4-methoxyphenyl)methyl]-5-methyl-, (1S,4S,5R)-rel- (CA INDEX NAME)

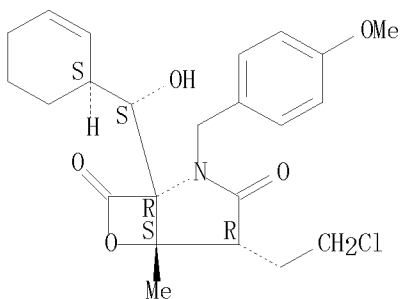
Relative stereochemistry.



RN 942517-09-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-2-[(4-methoxyphenyl)methyl]-5-methyl-, (1S,4S,5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



OS.CITING REF COUNT: 42 THERE ARE 42 CAPLUS RECORDS THAT CITE THIS RECORD (42 CITINGS)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 123 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:343706 CAPLUS  
DOCUMENT NUMBER: 147:108633  
TITLE: Targeted therapy of multiple myeloma based upon  
tumor-microenvironmental interactions  
AUTHOR(S): Anderson, Kenneth C.  
CORPORATE SOURCE: The Jerome Lipper Multiple Myeloma Center, Department  
of Medical Oncology, Dana-Farber Cancer Institute,  
Harvard Medical School, Boston, MA, USA  
SOURCE: Experimental Hematology (New York, NY, United States)  
(2007), 35(4, Suppl. 1), 155-162  
CODEN: EXHMA6; ISSN: 0301-472X  
PUBLISHER: Elsevier Inc.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

A review. Multiple myeloma (MM) remains incurable, but recent advances in genomics and proteomics have allowed for advances in our understanding of disease pathogenesis, identified novel therapeutic targets, allowed for mol. classification, and provided the scientific rationale for combining targeted therapies to increase tumor cell cytotoxicity and abrogate drug resistance. Besides these advances, recognition of the role of the bone marrow (BM) milieu in conferring growth, survival, and drug resistance in MM cells, both in laboratory and animal models, has allowed for the establishment of a new treatment paradigm targeting the tumor cell and its microenvironment to overcome drug resistance and improve patient outcomes in MM. In particular, thalidomide, bortezomib, and lenalidamide all overcome conventional drug resistance, not only by directly inducing tumor cell cytotoxicity, but by inhibiting adhesion of MM cells to BM. This abrogates constitutive and MM-binding-induced transcription and secretion of cytokines, inhibits angiogenesis, and augments host anti-MM immunity. These three drugs have rapidly translated from bench to bedside and in treatment protocols of MM, first in patients with relapsed refractory disease, and then alone and in combination in newly diagnosed patients. Promising novel targeted agents include the novel proteasome inhibitor NPI-0052 and the heat shock protein inhibitor KOS-953. Importantly, gene-array, proteomic, and cell-signaling studies have not only helped to identify in vivo mechanisms of action and drug resistance to novel agents, but also aided in the design of promising combination-therapy protocols.

IT **437742-34-2**, NPI-0052

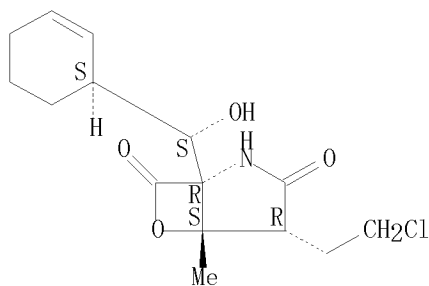
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)

(tumor-microenvironmental interaction-based targeted therapy using  
novel proteasome inhibitor, NPI-0052 alone or in combination with  
antitumor agents help overcome drug resistance and effectively treat  
patient with multiple myeloma)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 32 THERE ARE 32 CAPLUS RECORDS THAT CITE THIS  
RECORD (32 CITINGS)  
REFERENCE COUNT: 133 THERE ARE 133 CITED REFERENCES AVAILABLE FOR  
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT



L6 ANSWER 124 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2007:313870 CAPLUS

DOCUMENT NUMBER: 147:1069

TITLE: Targeting mitochondrial factor Smac/DIABLO as therapy for multiple myeloma (MM)

AUTHOR(S): Chauhan, Dharminder; Neri, Paola; Velankar, Mugdha; Podar, Klaus; Hideshima, Teru; Fulciniti, Mariateresa; Tassone, Pierfrancesco; Raje, Noopur; Mitsiades, Constantine; Mitsiades, Nicholas; Richardson, Paul; Zawel, Leigh; Tran, Mary; Munshi, Nikhil; Anderson, Kenneth C.

CORPORATE SOURCE: The Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

SOURCE: Blood (2007), 109(3), 1220-1227

CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: American Society of Hematology

DOCUMENT TYPE: Journal

LANGUAGE: English

## ABSTRACT:

Second mitochondria-derived activator of caspases (Smac) promotes apoptosis via activation of caspases. Here we show that a low-mol.-weight Smac mimetic LBW242 induces apoptosis in multiple myeloma (MM) cells resistant to conventional and bortezomib therapies. Examination of purified patient MM cells demonstrated similar results, without significant cytotoxicity against normal lymphocytes and bone marrow stromal cells (BMSCs). Importantly, LBW242 abrogates paracrine MM cell growth triggered by their adherence to BMSCs and overcomes MM cell growth and drug-resistance conferred by interleukin-6 or insulin-like growth factor-1. Overexpression of Bcl-2 similarly does not affect LBW242-induced cytotoxicity. Mechanistic studies show that LBW242-induced apoptosis in MM cells is associated with activation of caspase-8, caspase-9, and caspase-3, followed by PARP cleavage. In human MM xenograft mouse models, LBW242 is well tolerated, inhibits tumor growth, and prolongs survival. Importantly, combining LBW242 with novel agents, including tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or the proteasome inhibitors bortezomib and NPI-0052, as well as with the conventional anti-MM agent melphalan, induces additive/synergistic anti-MM activity. Our study therefore provides the rationale for clin. protocols evaluating LBW242, alone and together with other anti-MM agents, to improve patient outcome in MM.

IT **437742-34-2**, NPI-0052

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

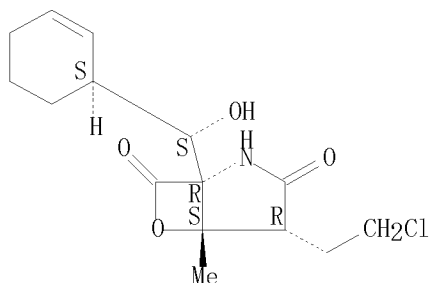
(targeting mitochondrial factor Smac/DIABLO as therapy for multiple myeloma)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,

4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 47 THERE ARE 47 CAPLUS RECORDS THAT CITE THIS RECORD (47 CITINGS)

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

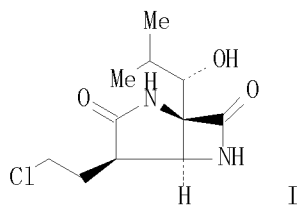
L6 ANSWER 125 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:287139 CAPLUS  
DOCUMENT NUMBER: 146:316677  
TITLE: Proteasome inhibiting beta-lactam compounds  
INVENTOR(S): Corey, Elias J.; Hogan, Philip C.  
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA  
SOURCE: U.S. Pat. Appl. Publ., 21 pp.  
CODEN: USXXCO  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070060561	A1	20070315	US 2005-224589	20050912
US 7465720	B2	20081216		
WO 2007033039	A2	20070322	WO 2006-US35196	20060908
WO 2007033039	A3	20071004		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
EP 1934257	A2	20080625	EP 2006-814408	20060908
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR			
PRIORITY APPLN. INFO.:			US 2005-224589 A 20050912	
			WO 2006-US35196 W 20060908	

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 146:316677; MARPAT 146:316677

GRAPHIC IMAGE:



#### ABSTRACT:

A total asym. synthesis of  $\beta$ -lactam I, an analog of salinosporamide A and omuralide both structurally and by its activity as a proteasome inhibitor, was disclosed. This  $\beta$ -lactam proteasome inhibitor is claimed for therapeutic use in the treatment of inflammation, ischemic or reperfusion injury and vascular occlusion occurring during a stroke.  $\beta$ -Lactam I was tested for inactivation of 20S proteasome.

IT 437742-34-2DP, Salinosporamide A, analogs

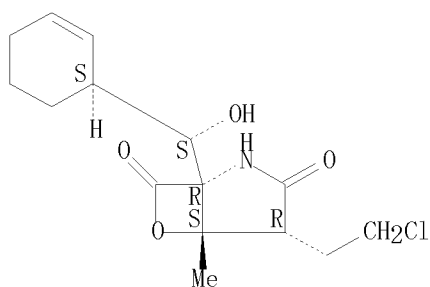
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(asym. synthesis of proteasome inhibiting  $\beta$ -lactams)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	1	THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT:	53	THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 126 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:282307 CAPLUS  
DOCUMENT NUMBER: 146:315181  
TITLE: Biosynthesis of salinosporamide A and its analogs  
INVENTOR(S): Lam, Kin Sing; Palladino, Michael  
PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
SOURCE: PCT Int. Appl., 271pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007030662	A1	20070315	WO 2006-US34930	20060908
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
US 20090197310	A1	20090806	US 2006-517899	20060908
US 7572606	B1	20090811		
PRIORITY APPLN. INFO. :			US 2005-715404P	P 20050909
			US 2006-816771P	P 20060626
			US 2006-816753P	P 20060626

## ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 146:315181; MARPAT 146:315181

## ABSTRACT:

Disclosed are methods of modulating biosynthesis of Salinosporamide A and its analogs, which are useful in treating cancer, inflammatory conditions, and/or infectious disease. The methods involve, for example, genetic manipulation, selection of reagents in the fermentation feedstock, and selection of fermentation conditions.

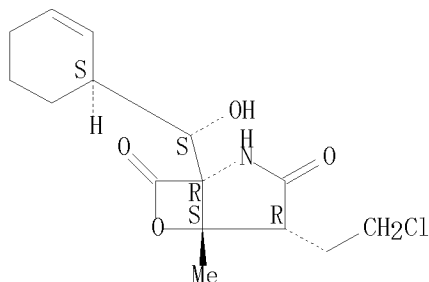
IT **437742-34-2P**, Salinosporamide A

RL: BMF (Bioindustrial manufacture); BSU (Biological study, unclassified); PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PRP (Properties); PUR (Purification or recovery); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses) (biosynthesis of salinosporamide and its analogs)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

IT **863126-95-8P** **872360-15-1P** **872360-16-2P**

RL: BMF (Bioindustrial manufacture); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); PUR

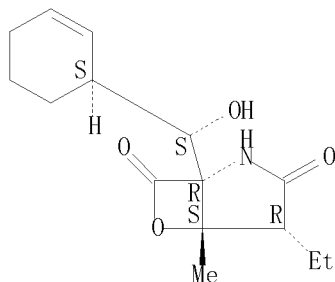


(Purification or recovery); RCT (Reactant); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent) (biosynthesis of salinosporamide and its analogs)

RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

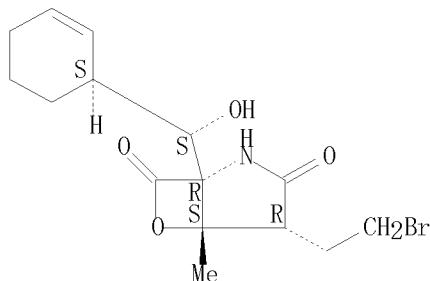
Absolute stereochemistry. Rotation (-).



RN 872360-15-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

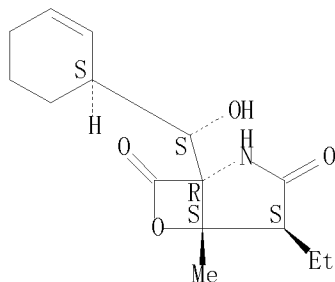
Absolute stereochemistry.



RN 872360-16-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4S,5S)-  
(CA INDEX NAME)

Absolute stereochemistry.



IT 823229-10-3P 823229-26-1P 855517-17-8P

872360-12-8P 872360-24-2P 928774-37-2P

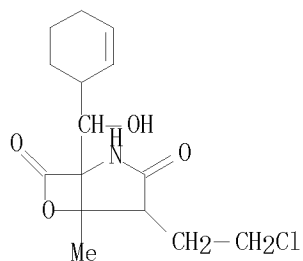
RL: BMF (Bioindustrial manufacture); BSU (Biological study, unclassified);  
PRP (Properties); PUR (Purification or recovery); BIOL (Biological study);  
PREP (Preparation)

(biosynthesis of salinosporamide and its analogs)

RN 823229-10-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-(2-cyclohexen-1-ylhydroxymethyl)-5-methyl- (CA INDEX

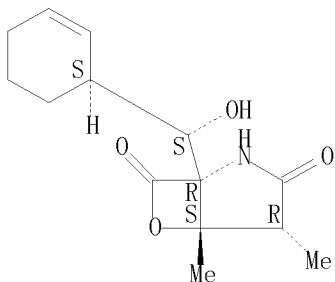
NAME)



RN 823229-26-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4R,5S)-  
(CA INDEX NAME)

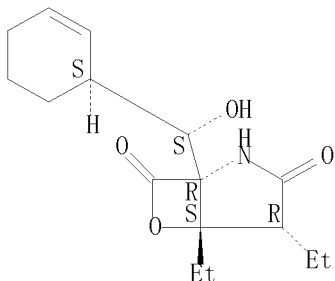
Absolute stereochemistry.



RN 855517-17-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-diethyl-, (1R,4R,5S)-  
(CA INDEX NAME)

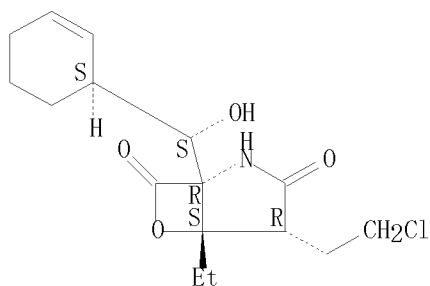
Absolute stereochemistry.



RN 872360-12-8 CAPLUS

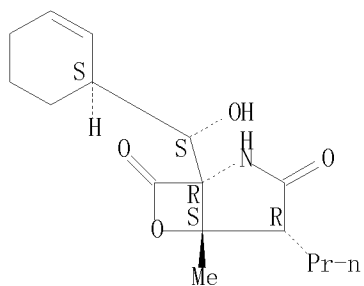
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-ethyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



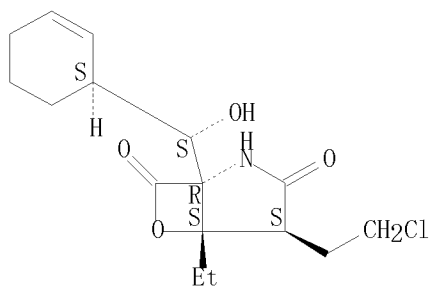
RN 872360-24-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



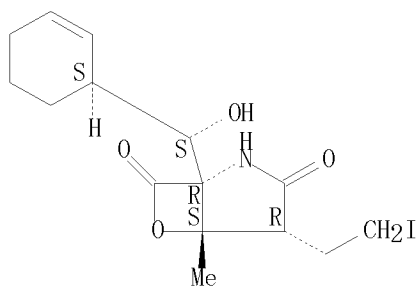
RN 928774-37-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-ethyl-,  
 (1R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT **823229-34-1P** **872360-17-3P**  
 RL: BSU (Biological study, unclassified); IMF (Industrial manufacture);  
 PEP (Physical, engineering or chemical process); PRP (Properties); PUR  
 (Purification or recovery); RCT (Reactant); BIOL (Biological study); PREP  
 (Preparation); PROC (Process); RACT (Reactant or reagent)  
 (biosynthesis of salinosporamide and its analogs)  
 RN 823229-34-1 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

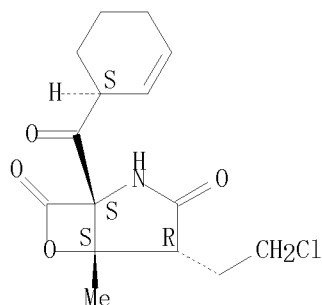
Absolute stereochemistry.



RN 872360-17-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
(1S, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



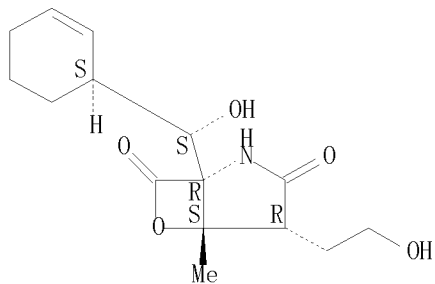
IT 823229-54-5P 823229-56-7P 872360-18-4P  
872360-22-0P 872360-23-1P

RL: BSU (Biological study, unclassified); IMF (Industrial manufacture);  
PRP (Properties); PUR (Purification or recovery); BIOL (Biological study);  
PREP (Preparation)  
(biosynthesis of salinosporamide and its analogs)

RN 823229-54-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

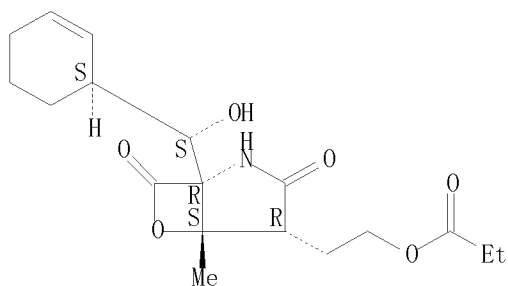
Absolute stereochemistry. Rotation (-).



RN 823229-56-7 CAPLUS

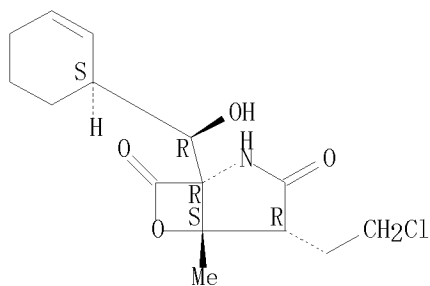
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-, (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



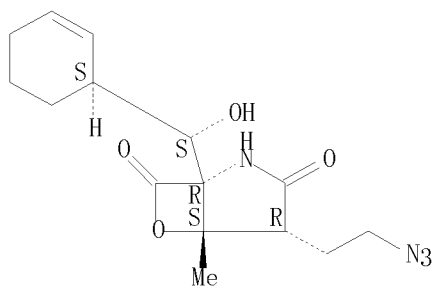
RN 872360-18-4 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



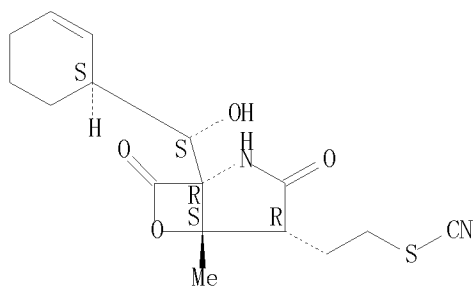
RN 872360-22-0 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-azidoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



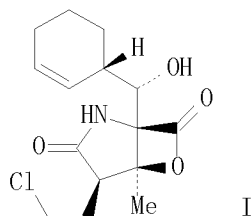
RN 872360-23-1 CAPLUS  
 CN Thiocyanic acid, 2-[(1R,4R,5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-  
 5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA  
 INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
(1 CITINGS)  
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 127 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:267227 CAPLUS  
 DOCUMENT NUMBER: 146:500762  
 TITLE: Stereoselective enzymatic reduction of  
 keto-salinosporamide to (-)-salinosporamide A  
 (NPI-0052)  
 AUTHOR(S): Manam, Rama Rao; Macherla, Venkat R.; Potts, Barbara  
 C. M.  
 CORPORATE SOURCE: Nereus Pharmaceuticals, Inc., San Diego, CA, 92121,  
 USA  
 SOURCE: Tetrahedron Letters (2007), 48(14), 2537-2540  
 CODEN: TELEAY; ISSN: 0040-4039  
 PUBLISHER: Elsevier Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 146:500762  
 GRAPHIC IMAGE:

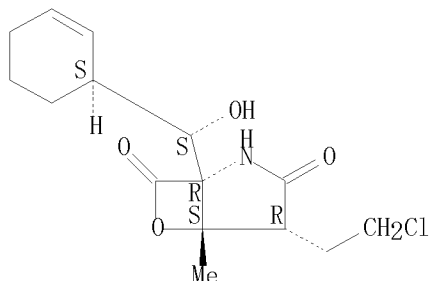


# ABSTRACT:

Salinosporamide A (NPI-0052, I), a highly potent 20S proteasome inhibitor, has been prepared from its ketone precursor by asym. enzymic reduction. The yields are quant. with complete stereoselective conversion to the desired product, with no evidence for the undesired diastereomer. This process should lead to new synthetic strategies for the total synthesis of I.

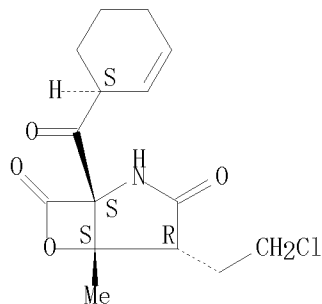
IT **437742-34-2P**, (-)-Salinosporamide A  
 RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP  
 (Preparation)  
 (preparation of (-)-salinosporamide A by stereoselective enzymic reduction of  
 keto-salinosporamide)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **872360-17-3**  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (preparation of (-)-salinosporamide A by stereoselective enzymic reduction of  
 keto-salinosporamide)  
 RN 872360-17-3 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
 (1S,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT:	8	THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
REFERENCE COUNT:	11	THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

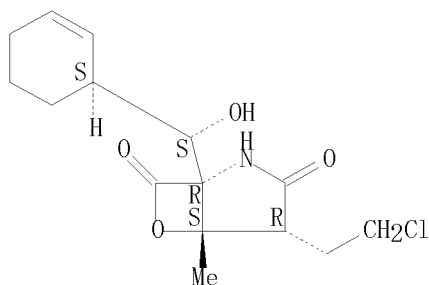


L6 ANSWER 128 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:238932 CAPLUS  
DOCUMENT NUMBER: 146:437661  
TITLE: Species-specific secondary metabolite production in  
marine actinomycetes of the genus Salinispora  
AUTHOR(S): Jensen, Paul R.; Williams, Philip G.; Oh, Dong-Chan;  
Zeigler, Lisa; Fenical, William  
CORPORATE SOURCE: Center for Marine Biotechnology and Biomedicine,  
Scripps Institution of Oceanography, University of  
California, San Diego, La Jolla, CA, 92093-0204, USA  
SOURCE: Applied and Environmental Microbiology (2007), 73(4),  
1146-1152  
CODEN: AEMIDF; ISSN: 0099-2240  
PUBLISHER: American Society for Microbiology  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
ABSTRACT:

Here we report assocns. between secondary metabolite production and phylogenetically distinct but closely related marine actinomycete species belonging to the genus Salinispora. The pattern emerged in a study that included global collection sites, and it indicates that secondary metabolite production can be a species-specific, phenotypic trait associated with broadly distributed bacterial populations. Assocns. between actinomycete phylotype and chemotype revealed an effective, diversity-based approach to natural product discovery that contradicts the conventional wisdom that secondary metabolite production is strain specific. The structural diversity of the metabolites observed, coupled with gene probing and phylogenetic analyses, implicates lateral gene transfer as a source of the biosynthetic genes responsible for compound production. These results conform to a model of selection-driven pathway fixation occurring subsequent to gene acquisition and provide a rare example in which demonstrable physiol. traits have been correlated to the fine-scale phylogenetic architecture of an environmental bacterial community.

IT 437742-34-2P, Salinosporamide A  
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP  
(Preparation)  
(secondary metabolite, production of; species-Specific secondary metabolite  
production in marine actinomycetes of the genus Salinispora)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

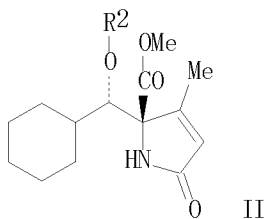
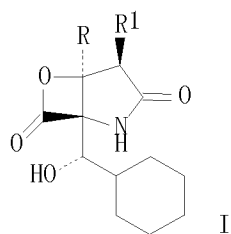


OS.CITING REF COUNT: 41 THERE ARE 41 CAPLUS RECORDS THAT CITE THIS  
RECORD (41 CITINGS)  
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 129 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:201546 CAPLUS  
DOCUMENT NUMBER: 146:274124  
TITLE: Preparation of analogs of salinosporamide A  
INVENTOR(S): Myers, Andrew G.; Sun, Binyuan; Jackson, Stona R.  
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA  
SOURCE: PCT Int. Appl., 75pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007021897	A1	20070222	WO 2006-US31314	20060810
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
EP 1931679	A1	20080618	EP 2006-789692	20060810
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR			
US 20090054665	A1	20090226	US 2008-28024	20080208
US 7691896	B2	20100406		
PRIORITY APPLN. INFO. :			US 2005-707021P	P 20050810
			WO 2006-US31314	W 20060810

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT  
OTHER SOURCE(S): CASREACT 146:274124; MARPAT 146:274124  
GRAPHIC IMAGE:

**ABSTRACT:**

Analog, such as I [R = CH<sub>2</sub>R<sub>3</sub>, R<sub>3</sub> = nucleophile; R<sub>1</sub> = alkyl, alkenyl, alkynyl, etc.], of salinosporamide A which will inhibit the proteasome, an intracellular enzyme complex that destroys proteins the cell no longer needs (no biol. testing data presented). Without the proteasome, proteins would build up and clog cellular machinery. Fast-growing cancer cells make especially heavy use of the proteasome, so thwarting its action is a compelling drug strategy. Thus, I [R = Me, R<sub>1</sub> = (CH<sub>2</sub>)<sub>2</sub>Cl] was prepared starting from (MeO) <sub>2</sub>POCH(NHCO<sub>2</sub>CMe<sub>3</sub>)CO<sub>2</sub>Me, Cl(CH<sub>2</sub>)<sub>2</sub>OSO<sub>2</sub>CF<sub>3</sub> and cyclohexanecarboxaldehyde via the pyrrolidinone intermediate II.

IT **437742-34-2P**, Salinosporamide A

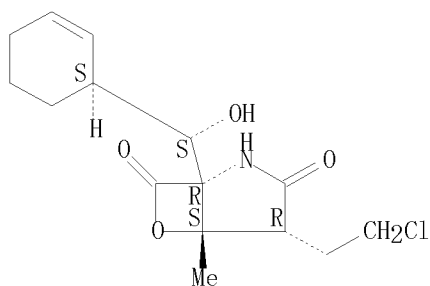
RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of analogs of salinosporamide A which inhibit proteasome and intracellular enzyme complex that destroys proteins cell no longer needs)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	1	THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT:	1	THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 130 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:175830 CAPLUS  
DOCUMENT NUMBER: 146:397994  
TITLE: Effects of halogens on the production of  
salinosporamides by the obligate marine actinomycete  
Salinispora tropica  
AUTHOR(S): Lam, Kin S.; Tsueng, Ginger; McArthur, Katherine A.;  
Mitchell, Scott S.; Potts, Barbara C. M.; Xu, Jianlin  
CORPORATE SOURCE: Nereus Pharmaceuticals, Inc., San Diego, CA, 92121,  
USA  
SOURCE: Journal of Antibiotics (2007), 60(1), 13-19  
CODEN: JANTAJ; ISSN: 0021-8820  
PUBLISHER: Japan Antibiotics Research Association  
DOCUMENT TYPE: Journal  
LANGUAGE: English

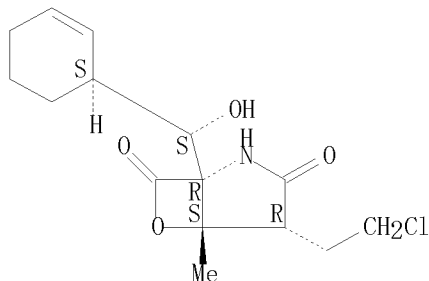
ABSTRACT:  
The authors examined the effects of halogens on the production of salinosporamide A (NPI-0052) by the obligate marine actinomycete *Salinispora tropica* NPS465, specifically the production of analogs containing halogens other than chlorine. Adding NaF, NaBr and NaI directly to the production medium prepared in seawater containing .apprx.3% NaCl did not induce the production of the corresponding analogs. Replacing seawater with 2-3% NaI in the production medium enhanced the production of NPI-0052 by 2.1 fold. Replacing seawater with 2-3% NaBr in the production medium suppressed the production of NPI-0052 but induced the production of a brominated analog at very low yield. Using a stepwise enrichment of bromide in the seed cultures in order to reduce the chloride ion carried over to the production medium, the production of the brominated analog was enhanced by 4 fold. The authors also demonstrated that the growth of this obligate marine actinomycete is dependent upon sodium concentration, not chloride concentration

IT 437742-34-2, Salinosporamide A 863126-95-8, NPI-0047  
872360-15-1, NPI 2053  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(effects of halogens on production of salinosporamides by marine  
actinomycete *Salinispora tropica*)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

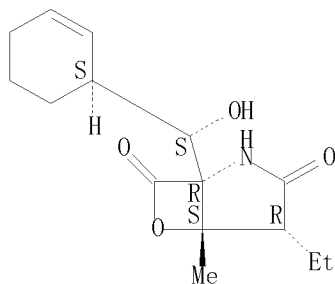
Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

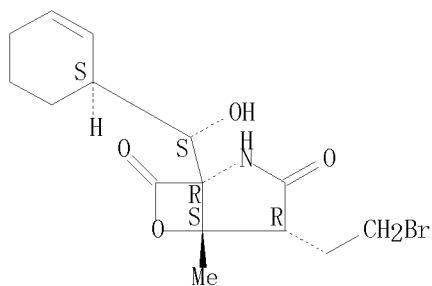
Absolute stereochemistry. Rotation (-).



RN 872360-15-1 CAPLUS

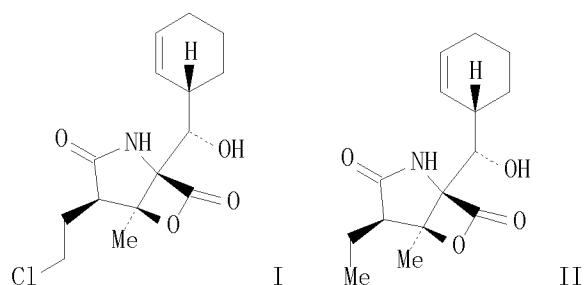
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT:	14	THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)
REFERENCE COUNT:	31	THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 131 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:126153 CAPLUS  
 DOCUMENT NUMBER: 146:354378  
 TITLE: Biosynthetic convergence of salinosporamides A and B  
 in the marine actinomycete *Salinispora tropica*  
 AUTHOR(S): Beer, Laura L.; Moore, Bradley S.  
 CORPORATE SOURCE: College of Pharmacy, University of Arizona, Tucson,  
 AZ, 85721, USA  
 SOURCE: Organic Letters (2007), 9(5), 845-848  
 CODEN: ORLEF7; ISSN: 1523-7060  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GRAPHIC IMAGE:

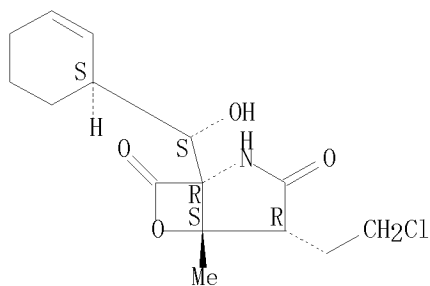


# ABSTRACT:

Feeding expts. with stable isotopes established that the potent 20S proteasome inhibitors salinosporamide A (I) and B (II) are biosynthesized in the marine bacterium *Salinispora tropica* from three biosynthetic building blocks, namely, acetate,  $\beta$ -hydroxy-2'-cyclohexenylalanine, and either butyrate or a tetrose-derived chlorinated mol. The unexpected observation that the chlorinated four-carbon residue in salinosporamide A is derived from a different metabolic origin than the nonchlorinated four-carbon unit in salinosporamide B is suggestive of a convergent biosynthesis to these two anticancer natural products.

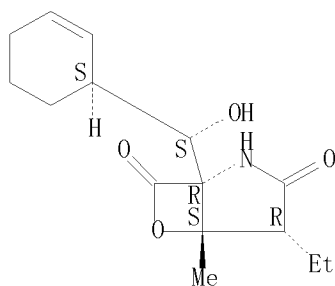
IT 437742-34-2, Salinosporamide A 863126-95-8,  
 Salinosporamide B  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (biosynthetic convergence of salinosporamides A and B in marine  
 actinomycete *Salinispora tropica*)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 27

THERE ARE 27 CAPLUS RECORDS THAT CITE THIS  
RECORD (28 CITINGS)

REFERENCE COUNT: 12

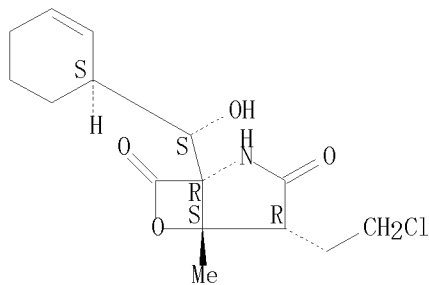
THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 132 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:111510 CAPLUS  
DOCUMENT NUMBER: 149:331755  
TITLE: Product class 6: lactones  
AUTHOR(S): Maier, M. E.  
CORPORATE SOURCE: Institut fuer Organische Chemie, Universitaet  
Tuebingen, Tuebingen, 72076, Germany  
SOURCE: Science of Synthesis (2006), 20b, 1421-1551  
CODEN: SSCYJ9  
PUBLISHER: Georg Thieme Verlag  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

A review of methods to prepare lactones and their applications to organic synthesis.

IT **437742-34-2P**  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(review preparation of lactones and their applications to organic synthesis)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 602 THERE ARE 602 CITED REFERENCES AVAILABLE FOR  
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

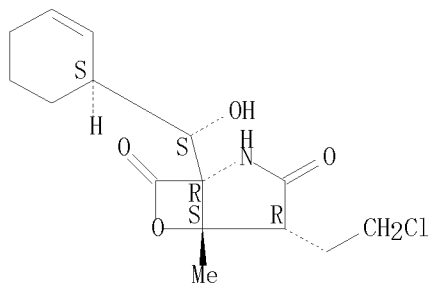


L6 ANSWER 133 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2007:94975 CAPLUS  
DOCUMENT NUMBER: 147:343803  
TITLE: Total synthesis of lactacystin and salinosporamide A  
AUTHOR(S): Shibasaki, Masakatsu; Kanai, Motomu; Fukuda, Nobuhisa  
CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, The  
University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo,  
113-0033, Japan  
SOURCE: Chemistry--An Asian Journal (2007), 2(1), 20-38  
CODEN: CAAJBI; ISSN: 1861-4728  
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

A review was presented of strategies directed toward the synthesis of lactacystin and salinosporamide A, which are fascinating mols. with regard to both their chemical structures and biol. activities. These naturally occurring compds. are potent and selective proteasome inhibitors. The mol. structures are characterized by their densely functionalized  $\gamma$ -lactam cores. The structure and biol. properties of these two compds. are attracting the attention of many chemists as challenging synthetic targets.

IT **437742-34-2P**, Salinosporamide A  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(review of asym. total synthesis of the naturally occurring  
 $\gamma$ -lactam proteasome inhibitors, lactacystin and salinosporamide  
A)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 43 THERE ARE 43 CAPLUS RECORDS THAT CITE THIS  
RECORD (43 CITINGS)  
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

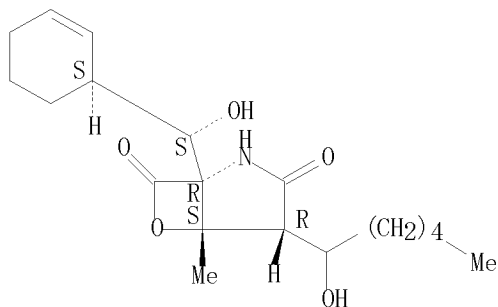
L6 ANSWER 134 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:85364 CAPLUS  
 DOCUMENT NUMBER: 146:333804  
 TITLE: Cinnabaramides A-G: Analogues of Lactacystin and Salinosporamide from a Terrestrial Streptomyces  
 AUTHOR(S): Stadler, Marc; Bitzer, Jens; Mayer-Bartschmid, Anke; Mueller, Hartwig; Benet-Buchholz, Jordi; Gantner, Florian; Tichy, Hans-Volker; Reinemer, Peter; Bacon, Kevin B.  
 CORPORATE SOURCE: InterMed Discovery GmbH (IMD), Dortmund, D-44227, Germany  
 SOURCE: Journal of Natural Products (2007), 70(2), 246-252  
 CODEN: JNPRDF; ISSN: 0163-3864  
 PUBLISHER: American Chemical Society-American Society of Pharmacognosy  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 ABSTRACT:

The cinnabaramides A-G were isolated from a terrestrial strain of Streptomyces as potent and selective inhibitors of the human 20S proteasome. Their chemical and biol. properties resemble those of salinosporamide A, a recently identified lead compound from an obligate marine actinomycete, which is currently under development as an anticancer agent. Cinnabaramides F and G combine essential structural features of salinosporamide A and lactacystin and show about equal potency in vitro, with IC50 values in the 1 nM range. The properties and phylogenetic position of the producer organism, the production and isolation of cinnabaramides A-G, their structure elucidation by MS and NMR, and their biol. activities are reported. Addnl., an x-ray crystal structure was obtained from cinnabaramide A.

IT 744200-67-7P, Cinnabaramide B 744200-68-8P,  
 Cinnabaramide C  
 RL: BSU (Biological study, unclassified); NPO (Natural product occurrence); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)  
 (cinnabaramides A-G, analogs of lactacystin and salinosporamide, isolated from terrestrial streptomyces as selective inhibitors of human 20S proteasome)

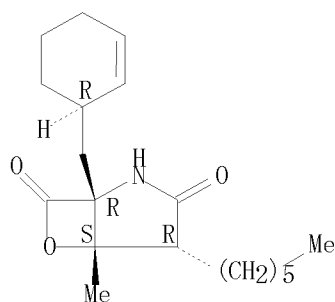
RN 744200-67-7 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-yl]hydroxymethyl]-4-(1-hydroxyhexyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 744200-68-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(1R)-2-cyclohexen-1-ylmethyl]-4-hexyl-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



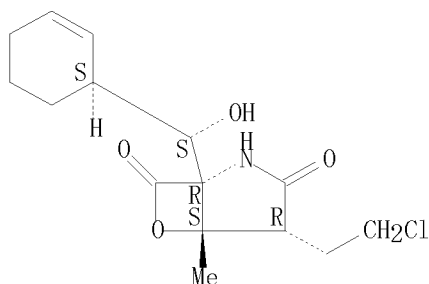
IT **437742-34-2P**, Salinosporamide A

RL: BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)  
(cinnabaramides A-G, analogs of lactacystin and salinosporamide, isolated from terrestrial streptomyces as selective inhibitors of human 20S proteasome)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



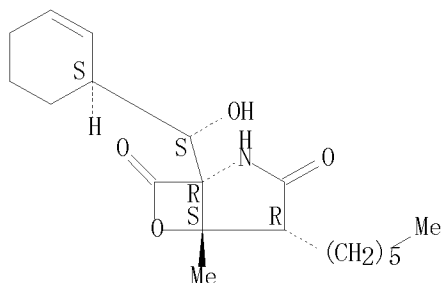
IT **744200-66-6P**, Cinnabaramide A

RL: BSU (Biological study, unclassified); NPO (Natural product occurrence); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)  
(isolation of, from terrestrial streptomyces and crystal structure of)

RN 744200-66-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 27 THERE ARE 27 CAPLUS RECORDS THAT CITE THIS RECORD (27 CITINGS)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 135 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:85345 CAPLUS  
 DOCUMENT NUMBER: 146:400610  
 TITLE: Salinosporamides D-J from the Marine Actinomycete  
 Salinispora tropica, Bromosalinosporamide, and  
 Thioester Derivatives Are Potent Inhibitors of the 20S  
 Proteasome  
 AUTHOR(S): Reed, Katherine A.; Manam, Rama Rao; Mitchell, Scott  
 S.; Xu, Jianlin; Teisan, Sy; Chao, Ta-Hsiang;  
 Deyanat-Yazdi, Gordafaried; Neuteboom, Saskia T. C.;  
 Lam, Kin S.; Potts, Barbara C. M.  
 CORPORATE SOURCE: Nereus Pharmaceuticals, Inc., San Diego, CA, 92121,  
 USA  
 SOURCE: Journal of Natural Products (2007), 70(2), 269-276  
 CODEN: JNPRDF; ISSN: 0163-3864  
 PUBLISHER: American Chemical Society-American Society of  
 Pharmacognosy  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 ABSTRACT:

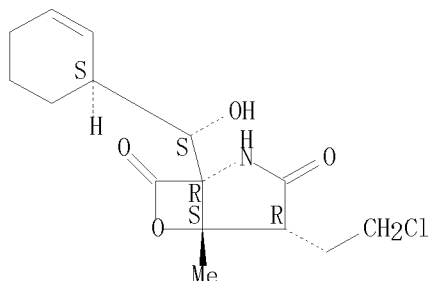
Salinosporamide A (NPI-0052; 3), a highly potent inhibitor of the 20S proteasome, is currently in phase I clin. trials for the treatment of cancer. During the course of purifying multigram quantities of 3 from Salinispora tropica fermentation exts., several new salinosporamides were isolated and characterized, most of which represent modifications to the chloroethyl substituent at C-2. Specifically, 3 was isolated along with the known compound salinosporamide B (4), the previously undescribed Me congener salinosporamide D (7), and C-2 epimers of 3 and 7 (salinosporamides F (9) and G (10), resp.). Salinosporamide I (13), in which the Me group at the ring junction is replaced with an Et group, and the C-5 deshydroxyl analog salinosporamide J (14), were also identified. Replacement of synthetic sea salt with sodium bromide in the fermentation media produced bromosalinosporamide (12), 4, and its C-2 epimer (11, salinosporamide H). In addition to these eight new salinosporamides, several thioester derivs. were generated semisynthetically. IC50 values for cytotoxicity against human multiple myeloma cell line RPMI 8226 and inhibition of the chymotrypsin-like (CT-L) activity of purified rabbit 20S proteasomes were determined for all compds. The results indicate that thioesters may directly inhibit the proteasome, albeit with reduced potency compared to their  $\beta$ -lactone counterparts.

IT 437742-34-2P, Salinosporamide A  
 RL: BMF (Bioindustrial manufacture); BSU (Biological study, unclassified);  
 NPO (Natural product occurrence); PEP (Physical, engineering or chemical  
 process); PRP (Properties); PUR (Purification or recovery); RCT  
 (Reactant); BIOL (Biological study); OCCU (Occurrence); PREP  
 (Preparation); PROC (Process); RACT (Reactant or reagent)  
 (salinosporamides D-J from Salinispora tropica, bromosalinosporamide,  
 and thioester derivs. are potent inhibitors of the 20S proteasome)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



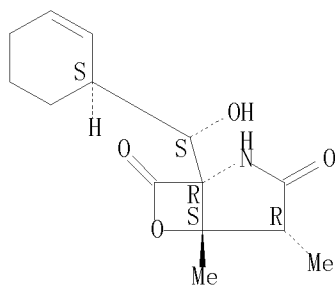
IT 823229-26-1P, Salinosporamide D 863126-95-8P,  
 Salinosporamide B 872360-11-7P, Salinosporamide F  
872360-12-8P, Salinosporamide I 872360-13-9P,  
 Salinosporamide G 872360-15-1P, Bromosalinosporamide

**872360-16-2P**, Salinosporamide H **872360-24-2P**,  
 Salinosporamide E **932739-03-2P**, Salinosporamide J  
 RL: BMF (Bioindustrial manufacture); BSU (Biological study, unclassified);  
 NPO (Natural product occurrence); PRP (Properties); PUR (Purification or  
 recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)  
 (salinosporamides D-J from *Salinispora tropica*, bromosalinosporamide,  
 and thioester derivs. are potent inhibitors of the 20S proteasome)

RN 823229-26-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

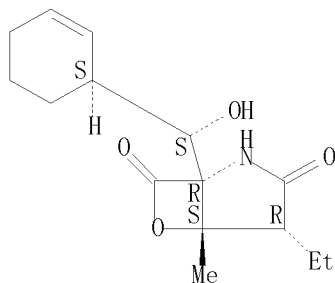
Absolute stereochemistry.



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

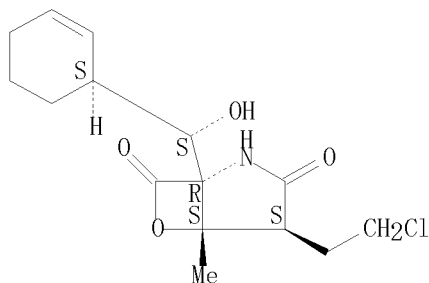
Absolute stereochemistry. Rotation (-).



RN 872360-11-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4S,5S)- (CA INDEX NAME)

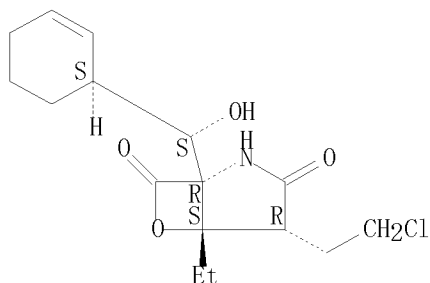
Absolute stereochemistry.



RN 872360-12-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-ethyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

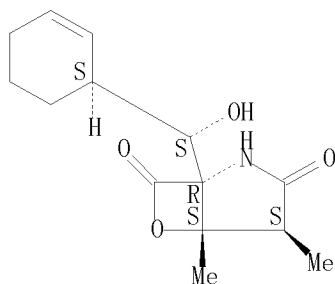
Absolute stereochemistry.



RN 872360-13-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4S,5S)-  
(CA INDEX NAME)

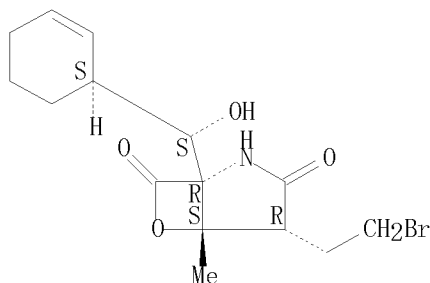
Absolute stereochemistry.



RN 872360-15-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

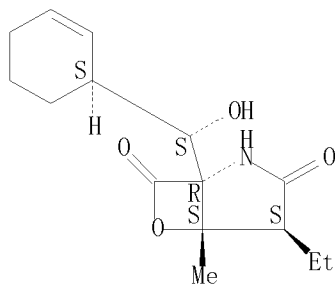
Absolute stereochemistry.



RN 872360-16-2 CAPLUS

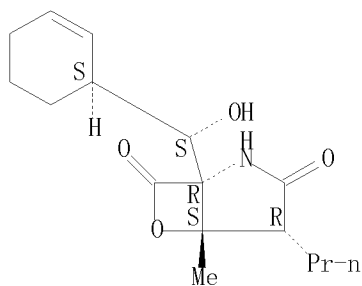
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4S,5S)-  
(CA INDEX NAME)

Absolute stereochemistry.



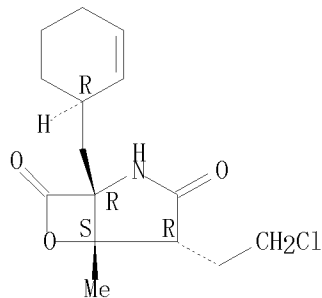
RN 872360-24-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-,  
 (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 932739-03-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(1R)-2-cyclohexen-1-ylmethyl]-5-methyl-, (1R, 4R, 5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



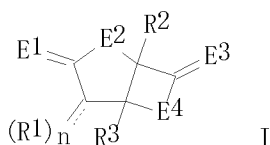
OS.CITING REF COUNT:	36	THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (36 CITINGS)
REFERENCE COUNT:	22	THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 136 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2007:17774 CAPLUS  
 DOCUMENT NUMBER: 146:100482  
 TITLE: Preparation [3.2.0] heterobicyclic analogs of  
 salinosporamide A for therapeutic use in the treatment  
 of cancer, inflammation and microbial infection  
 INVENTOR(S): Palladino, Michael; Potts, Barbara Christine;  
 Macherla, Venkata Rami Reddy; Neuteboom, Saskia  
 Theodora Cornelia  
 PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
 SOURCE: U.S. Pat. Appl. Publ., 122 pp., Cont.-in-part of U.S.  
 Ser. No. 412,476.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 5  
 PATENT INFORMATION:

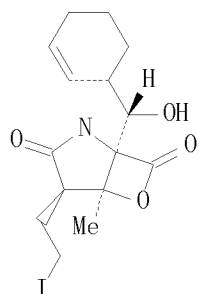
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070004676	A1	20070104	US 2006-453374	20060615
US 7579371	B2	20090825		
US 20050288352	A1	20051229	US 2005-118260	20050429
US 7276530	B2	20071002		
AU 2005283141	A1	20060316	AU 2005-283141	20050429
CA 2565235	A1	20060316	CA 2005-2565235	20050429
EP 1812443	A2	20070801	EP 2005-818192	20050429
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU				
BR 2005009824	A	20071009	BR 2005-9824	20050429
CN 101061120	A	20071024	CN 2005-80019345	20050429
JP 2007535559	T	20071206	JP 2007-511021	20050429
EP 2025679	A2	20090218	EP 2008-168314	20050429
EP 2025679	A3	20090708		
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
EP 2266988	A1	20101229	EP 2010-179249	20050429
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
US 20060264495	A1	20061123	US 2006-412476	20060427
MX 2006012421	A	20070131	MX 2006-12421	20061026
ZA 2006009778	A	20091028	ZA 2006-9778	20061123
KR 2007016158	A	20070207	KR 2006-7025184	20061129
PRIORITY APPLN. INFO.:			US 2004-567336P	P 20040430
			US 2004-580838P	P 20040618
			US 2004-591190P	P 20040726
			US 2004-627462P	P 20041112
			US 2005-644132P	P 20050113
			US 2005-659385P	P 20050304
			US 2005-118260	A2 20050429
			US 2005-676533P	P 20050429
			US 2006-412476	A2 20060427
			EP 2005-818192	A3 20050429
			EP 2008-168314	A3 20050429
			WO 2005-US14846	W 20050429

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT  
 OTHER SOURCE(S): CASREACT 146:100482; MARPAT 146:100482  
 GRAPHIC IMAGE:

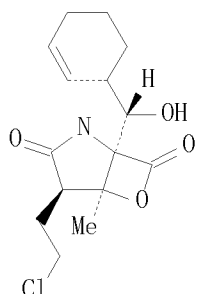




I



II



III

**ABSTRACT:**

[3.2.0]-Bicycloheptanes I [R1 = H, halo, (un)substituted alkyl, etc.; R2 = H, halo, (un)substituted alkyl, alkenyl, etc.; R3 = halo, (un)substituted aryl, cycloalkyl, etc.; E1-4 independently = (un)substituted heteroatom; with provisions] and derivs. thereof, are prepared and disclosed as having anti-cancer, anti-inflammatory, and anti-microbial properties. Thus, e.g., II was prepared by iodination of fermentation product III. In assays of growth inhibition of human multiple myeloma, II for example demonstrated EC50 values (nM) of 5.9 and 3.2 resp. against RPMI 8226 and U266 cell lines. Pharmaceutical compns. comprising such compds. and methods of treating cancer, inflammatory conditions, and microbial infections with the disclosed compds. or the disclosed pharmaceutical compns. are also disclosed.

**IT 872360-11-7P**

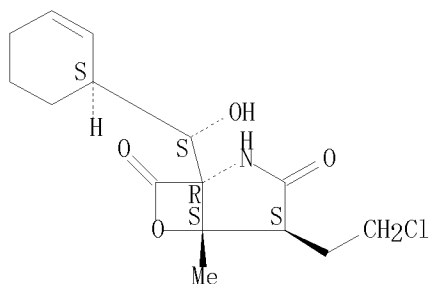
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of salinosporamide A oxazabicycloheptane analogs obtained via fermentation process as proteinase inhibitors for treatment of cancer, inflammatory conditions, and microbial infections)

RN 872360-11-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

**IT 872360-17-3P 872360-18-4P**

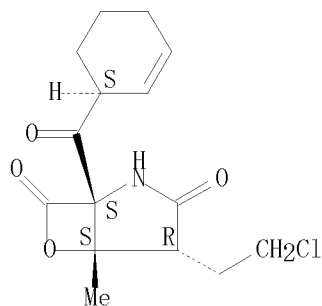
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of salinosporamide A oxazabicycloheptane analogs obtained via fermentation process as proteinase inhibitors for treatment of cancer, inflammatory conditions, and microbial infections)

RN 872360-17-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
(1S,4R,5S)- (CA INDEX NAME)

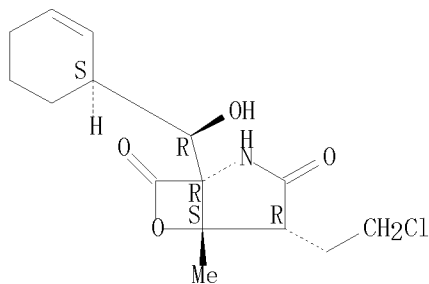
Absolute stereochemistry.



RN 872360-18-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



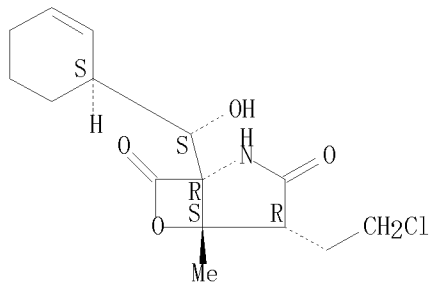
IT 437742-34-2P 863126-95-8P 872360-15-1P

RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of salinosporamide A oxazabicycloheptane analogs obtained via fermentation process as proteinase inhibitors for treatment of cancer, inflammatory conditions, and microbial infections)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

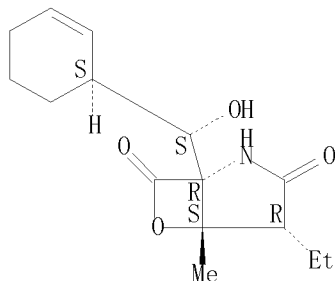
Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

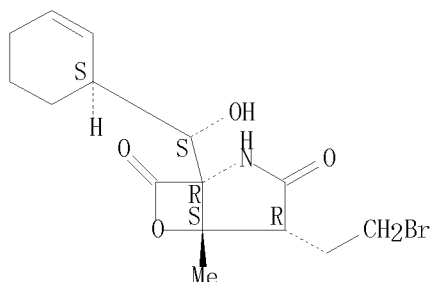
Absolute stereochemistry. Rotation (-).



RN 872360-15-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 823229-34-1P 823229-54-5P 823229-56-7P  
872360-22-0P 872360-23-1P 872360-24-2P

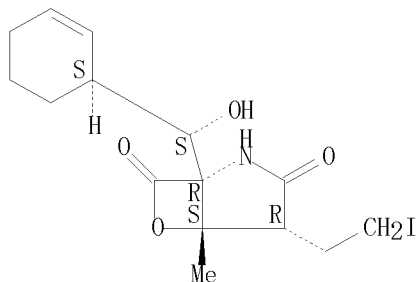
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN  
(Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);  
PREP (Preparation); USES (Uses)

(preparation of salinosporamide A oxazabicycloheptane analogs obtained via  
fermentation process as proteinase inhibitors for treatment of cancer,  
inflammatory conditions, and microbial infections)

RN 823229-34-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

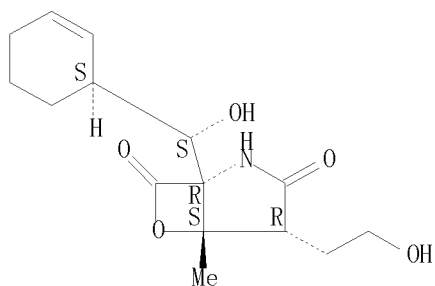
Absolute stereochemistry.



RN 823229-54-5 CAPLUS

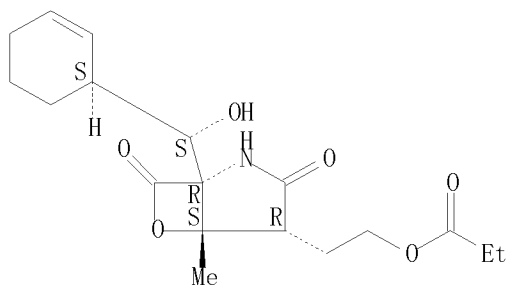
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



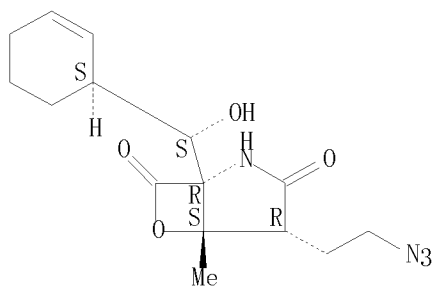
RN 823229-56-7 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



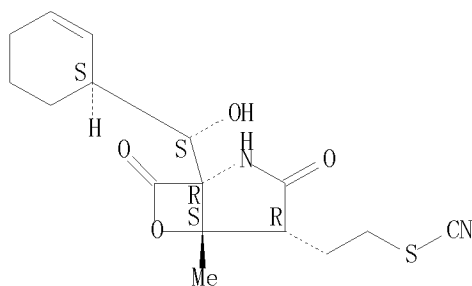
RN 872360-22-0 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-azidoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 872360-23-1 CAPLUS  
 CN Thiocyanic acid, 2-[(1R,4R,5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA INDEX NAME)

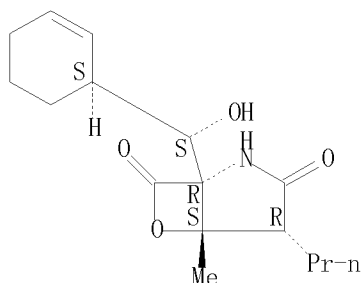
Absolute stereochemistry.



RN 872360-24-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 823229-26-1P 872360-12-8P 872360-13-9P

872360-14-0P 872360-16-2P

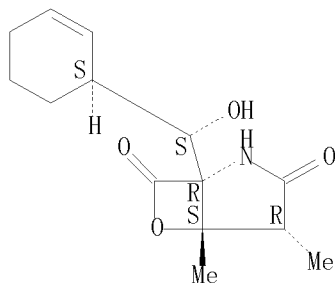
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
(Uses)

(preparation of salinosporamide A oxazabicycloheptane analogs obtained via  
fermentation process as proteinase inhibitors for treatment of cancer,  
inflammatory conditions, and microbial infections)

RN 823229-26-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R, 4R, 5S)-  
(CA INDEX NAME)

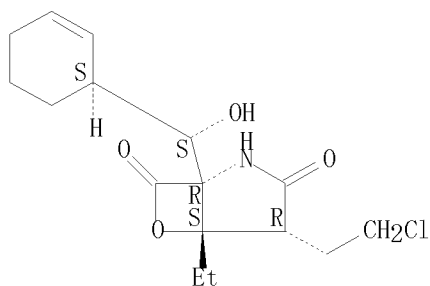
Absolute stereochemistry.



RN 872360-12-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-ethyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

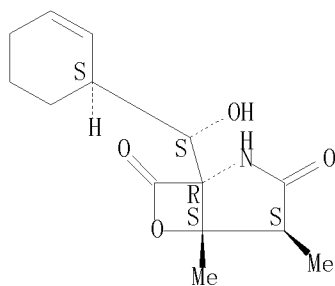
Absolute stereochemistry.



RN 872360-13-9 CAPLUS

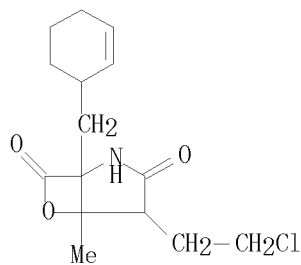
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4S,5S)-  
(CA INDEX NAME)

Absolute stereochemistry.



RN 872360-14-0 CAPLUS

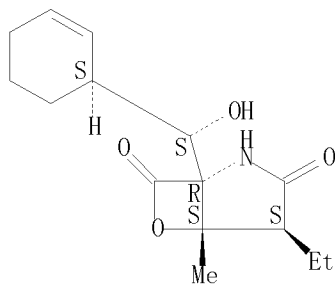
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-(2-cyclohexen-1-ylmethyl)-5-methyl-, (1R,4S,5S)-  
(CA INDEX NAME)



RN 872360-16-2 CAPLUS

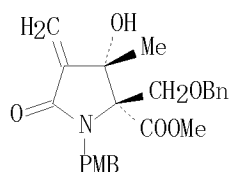
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4S,5S)-  
(CA INDEX NAME)

Absolute stereochemistry.





L6 ANSWER 137 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2006:1323505 CAPLUS  
 DOCUMENT NUMBER: 146:229069  
 TITLE: Stereoselective formal synthesis of the potent  
 proteasome inhibitor: salinosporamide A  
 AUTHOR(S): Caubert, Virginie; Masse, Julien; Retailleau, Pascal;  
 Langlois, Nicole  
 CORPORATE SOURCE: CNRS, Institut de Chimie des Substances Naturelles,  
 Gif-sur-Yvette, 91198, Fr.  
 SOURCE: Tetrahedron Letters (2006), Volume Date 2007, 48(3),  
 381-384  
 CODEN: TELEAY; ISSN: 0040-4039  
 PUBLISHER: Elsevier Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 146:229069  
 GRAPHIC IMAGE:



I

## ABSTRACT:

(2R,3S)- $\alpha$ -Methylene lactam I (PMB = 4-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>), the key intermediate in Corey's syntheses of salinosporamide A, was synthesized from (S)-2-(hydroxymethyl)pyroglutamate through chemoselective O-protection, regio- and stereoselective N-methylnitrone cycloaddn., and quaternization-elimination reactions as the main steps.

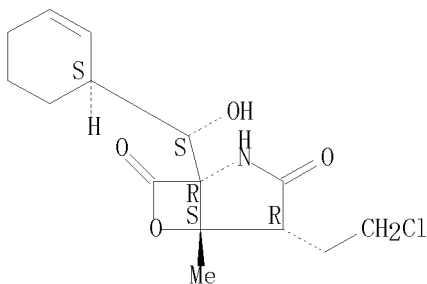
IT **437742-34-2P**, Salinosporamide A

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (asym. formal synthesis of salinosporamide A from  
 (hydroxymethyl)pyroglutamate via regio- and stereoselective  
 N-methylnitrone cycloaddn.)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 33 THERE ARE 33 CAPLUS RECORDS THAT CITE THIS  
 RECORD (33 CITINGS)  
 REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

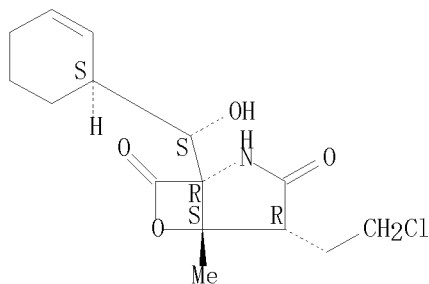


L6 ANSWER 138 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2006:1323341 CAPLUS  
DOCUMENT NUMBER: 146:308599  
TITLE: Comparison of biochemical and biological effects of  
ML858 (salinosporamide A) and bortezomib  
AUTHOR(S): Williamson, Mark J.; Blank, Jonathan L.; Bruzzese,  
Frank J.; Cao, Yueying; Daniels, J. Scott; Dick,  
Lawrence R.; Labutti, Jason; Mazzola, Anne M.; Patil,  
Ashok D.; Reimer, Corinne L.; Solomon, Marjorie S.;  
Stirling, Matthew; Tian, Yuan; Tsu, Christopher A.;  
Weatherhead, Gabriel S.; Zhang, Julie X.; Rolfe, Mark  
CORPORATE SOURCE: Millennium Pharmaceuticals, Inc., Cambridge, MA, USA  
SOURCE: Molecular Cancer Therapeutics (2006), 5(12), 3052-3061  
CODEN: MCTOCF; ISSN: 1535-7163  
PUBLISHER: American Association for Cancer Research  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
ABSTRACT:

Strains within the genus *Salinospora* have been shown to produce complex natural products having antibiotic and antiproliferative activities. The biochem. basis for the cytotoxic effects of salinosporamide A has been linked to its ability to inhibit the proteasome. Synthetically accessible salinosporamide A (ML858) was used to determine its biochem. and biol. activities and to compare its effects with those of bortezomib. ML858 and bortezomib show time- and concentration-dependent inhibition of the proteasome in vitro. However, unlike bortezomib, which is a reversible inhibitor, ML858 covalently binds to the proteasome, resulting in the irreversible inhibition of 20S proteasome activity. ML858 was equipotent to bortezomib in cell-based reporter stabilization assays, but due to intramol. instability is less potent in long-term assays. ML858 failed to maintain levels of proteasome inhibition necessary to achieve efficacy in tumor models responsive to bortezomib. Our results show that ML858 and bortezomib exhibit different kinetic and pharmacol. profiles and suggest that addnl. characterization of ML858 is warranted before its therapeutic potential can be fully appreciated.

IT **437742-34-2**, Salinosporamide A  
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(comparison of biochem. and biol. effects of ML858 (salinosporamide A) and bortezomib)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



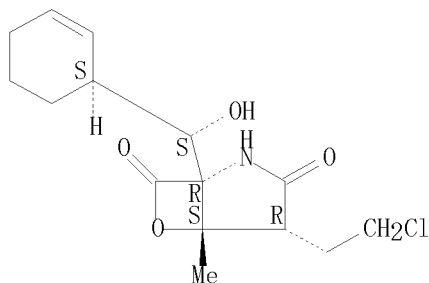
OS.CITING REF COUNT: 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS  
RECORD (17 CITINGS)  
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 139 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2006:1236222 CAPLUS  
DOCUMENT NUMBER: 146:220358  
TITLE: NPI-0052 enhances tumoricidal response to conventional cancer therapy in a colon cancer model  
AUTHOR(S): Cusack, James C., Jr.; Liu, Rong; Xia, Lijun; Chao, Ta-Hsiang; Pien, Christine; Niu, Wei; Palombella, Vito J.; Neuteboom, Saskia T. C.; Palladino, Michael A.  
CORPORATE SOURCE: Division of Surgical Oncology, Massachusetts General Hospital, Boston, 02114, USA  
SOURCE: Clinical Cancer Research (2006), 12(22), 6758-6764  
CODEN: CCREF4; ISSN: 1078-0432  
PUBLISHER: American Association for Cancer Research  
DOCUMENT TYPE: Journal  
LANGUAGE: English

ABSTRACT:  
In the current study, we examine the effects of a novel proteasome inhibitor, NPI-0052 (salinosporamide A), on proteasome function and nuclear factor- $\kappa$ B activation and evaluate its ability to enhance treatment response in colon cancer xenografts when administered orally. The effects of treatment on nuclear factor- $\kappa$ B activation, cell cycle regulation, and apoptosis were determined. The pharmacodynamic effect of NPI-0052 on 20S proteasome function was assayed in vivo following oral and i.v. drug administration and compared with treatment with bortezomib. The effect of combined treatment with chemotherapy was determined in a colon cancer xenograft model. We found that NPI-0052 is a potent, well-tolerated proteasome inhibitor that has pharmacodynamic properties distinct from bortezomib in that it achieves significantly higher and more sustained levels of proteasome inhibition. When combined with chemotherapy, NPI-0052 increases apoptosis and shifts cells toward G2 cell cycle arrest. When added to chemotherapy in vivo [using combinations of 5-fluorouracil (5-FU), CPT-11, Avastin (bevacizumab), leucovorin, and oxaliplatin], NPI-0052 significantly improved the tumoricidal response and resulted in a 1.8-fold increased response to CPT-11, 5-FU, and leucovorin triple-drug combination ( $P = 0.0002$ ,  $t$  test), a 1.5-fold increased response to the oxaliplatin, 5-FU, and leucovorin triple-drug combination ( $P = 0.013$ ,  $t$  test), and a 2.3-fold greater response to the CPT-11, 5-FU, leucovorin, and Avastin regimen ( $P = 0.00057$ ). The high level of proteasome inhibition achieved by NPI-0052 is well tolerated and significantly improves the tumoricidal response to multidrug treatment in a colon cancer xenograft model. Further evaluation of this novel proteasome inhibitor in clin. trials is indicated.

IT 437742-34-2, NPI-0052  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(NPI-0052-mediated improvement in tumoricidal response to multidrug treatment in colon cancer model)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



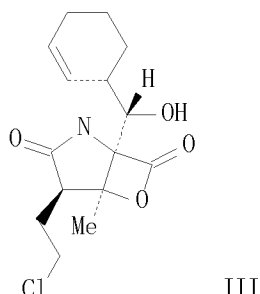
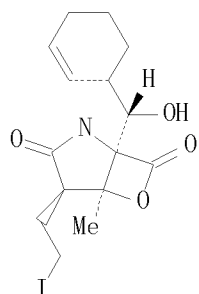
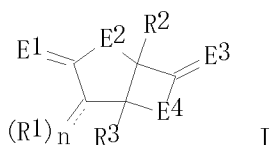
OS.CITING REF COUNT: 42 THERE ARE 42 CAPLUS RECORDS THAT CITE THIS RECORD (42 CITINGS)  
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 140 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2006:1228634 CAPLUS  
 DOCUMENT NUMBER: 146:7752  
 TITLE: Preparation [3.2.0] heterobicyclic analogs of  
 salinosporamide A for therapeutic use in the treatment  
 of cancer, inflammation and microbial infection  
 INVENTOR(S): Palladino, Michael; Potts, Barbara Christine;  
 Macherla, Venkata Rami Reddy; Neuteboom, Saskia  
 Theodora Cornelia  
 PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
 SOURCE: U.S. Pat. Appl. Publ., 121 pp., Cont.-in-part of U.S.  
 Ser. No. 118,260.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 5  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060264495	A1	20061123	US 2006-412476	20060427
US 20050288352	A1	20051229	US 2005-118260	20050429
US 7276530	B2	20071002		
AU 2005283141	A1	20060316	AU 2005-283141	20050429
CA 2565235	A1	20060316	CA 2005-2565235	20050429
EP 1812443	A2	20070801	EP 2005-818192	20050429
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU				
BR 2005009824	A	20071009	BR 2005-9824	20050429
CN 101061120	A	20071024	CN 2005-80019345	20050429
JP 2007535559	T	20071206	JP 2007-511021	20050429
EP 2025679	A2	20090218	EP 2008-168314	20050429
EP 2025679	A3	20090708		
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
EP 2266988	A1	20101229	EP 2010-179249	20050429
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
US 20070004676	A1	20070104	US 2006-453374	20060615
US 7579371	B2	20090825		
MX 2006012421	A	20070131	MX 2006-12421	20061026
ZA 2006009778	A	20091028	ZA 2006-9778	20061123
KR 2007016158	A	20070207	KR 2006-7025184	20061129
PRIORITY APPLN. INFO.:			US 2004-567336P	P 20040430
			US 2004-580838P	P 20040618
			US 2004-591190P	P 20040726
			US 2004-627462P	P 20041112
			US 2005-644132P	P 20050113
			US 2005-659385P	P 20050304
			US 2005-118260	A2 20050429
			US 2005-676533P	P 20050429
			EP 2005-818192	A3 20050429
			EP 2008-168314	A3 20050429
			WO 2005-US14846	W 20050429
			US 2006-412476	A2 20060427

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT  
 OTHER SOURCE(S): CASREACT 146:7752; MARPAT 146:7752  
 GRAPHIC IMAGE:

**ABSTRACT:**

[3.2.0]-Bicycloheptanes I [R1 = H, halo, (un)substituted alkyl, etc.; R2 = H, halo, (un)substituted alkyl, alkenyl, etc.; R3 = halo, (un)substituted aryl, cycloalkyl, etc.; E1-4 independently = (un)substituted heteroatom; with provisions] and derivs. thereof, are prepared and disclosed as having anti-cancer, anti-inflammatory, and anti-microbial properties. Thus, e.g., II was prepared by iodination of fermentation product III. In assays of growth inhibition of human multiple myeloma, II for example demonstrated EC50 values (nM) of 5.9 and 3.2 resp. against RPMI 8226 and U266 cell lines. Pharmaceutical compns. comprising such compds. and methods of treating cancer, inflammatory conditions, and microbial infections with the disclosed compds. or the disclosed pharmaceutical compns. are also disclosed.

**IT 872360-11-7P**

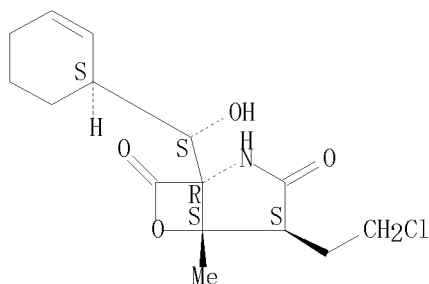
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of salinosporamide A oxazabicycloheptane analogs obtained via fermentation process as proteinase inhibitors for treatment of cancer, inflammatory conditions, and microbial infections)

RN 872360-11-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

**IT 872360-17-3P 872360-18-4P**

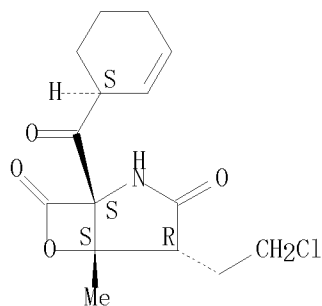
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of salinosporamide A oxazabicycloheptane analogs obtained via fermentation process as proteinase inhibitors for treatment of cancer, inflammatory conditions, and microbial infections)

RN 872360-17-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
(1S,4R,5S)- (CA INDEX NAME)

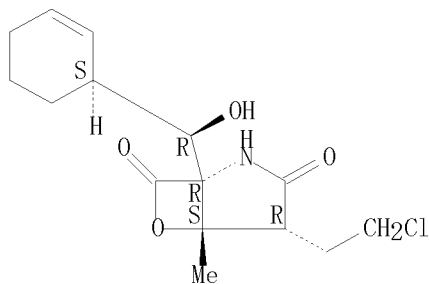
Absolute stereochemistry.



RN 872360-18-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



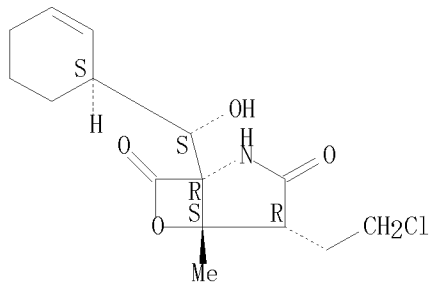
IT 437742-34-2P, Salinosporamide A 863126-95-8P  
872360-15-1P

RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of salinosporamide A oxazabicycloheptane analogs obtained via fermentation process as proteinase inhibitors for treatment of cancer, inflammatory conditions, and microbial infections)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

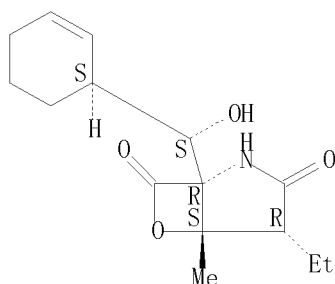
Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

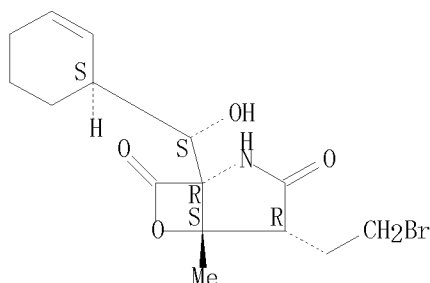
Absolute stereochemistry. Rotation (-).



RN 872360-15-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 823229-34-1P 823229-54-5P 823229-56-7P  
872360-22-0P 872360-23-1P 872360-24-2P

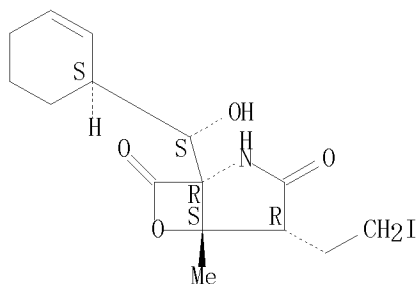
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN  
(Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);  
PREP (Preparation); USES (Uses)

(preparation of salinosporamide A oxazabicycloheptane analogs obtained via  
fermentation process as proteinase inhibitors for treatment of cancer,  
inflammatory conditions, and microbial infections)

RN 823229-34-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

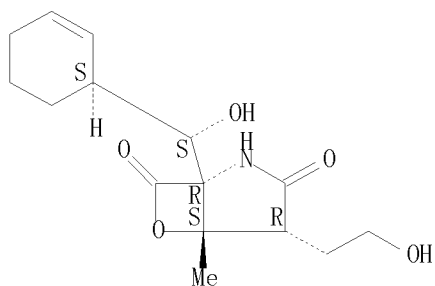
Absolute stereochemistry.



RN 823229-54-5 CAPLUS

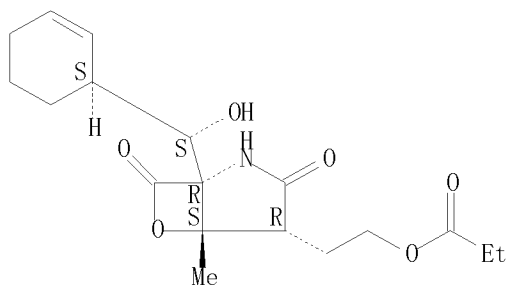
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



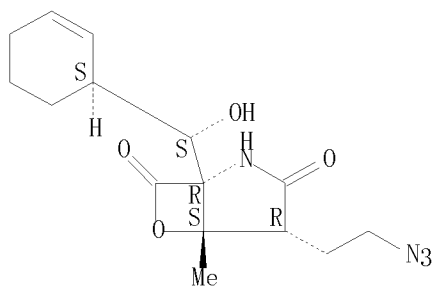
RN 823229-56-7 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 872360-22-0 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-azidoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

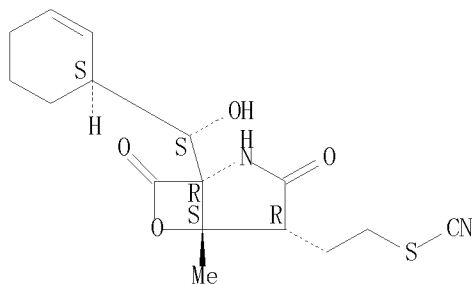
Absolute stereochemistry.



RN 872360-23-1 CAPLUS  
 CN Thiocyanic acid, 2-[(1R,4R,5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA INDEX NAME)

Absolute stereochemistry.

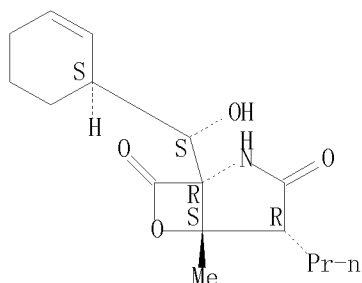




RN 872360-24-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 823229-26-1P 872360-12-8P 872360-13-9P

872360-14-0P 872360-16-2P

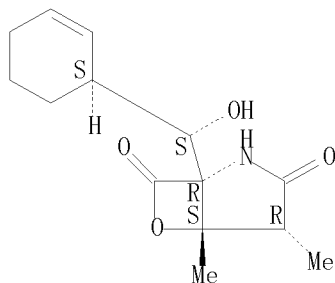
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
(Uses)

(preparation of salinosporamide A oxazabicycloheptane analogs obtained via  
fermentation process as proteinase inhibitors for treatment of cancer,  
inflammatory conditions, and microbial infections)

RN 823229-26-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R, 4R, 5S)-  
(CA INDEX NAME)

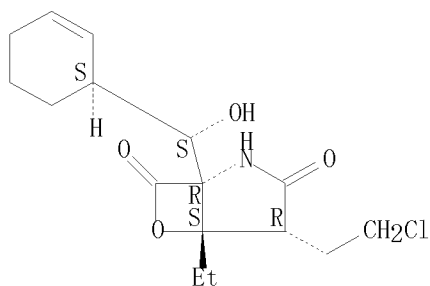
Absolute stereochemistry.



RN 872360-12-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-ethyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

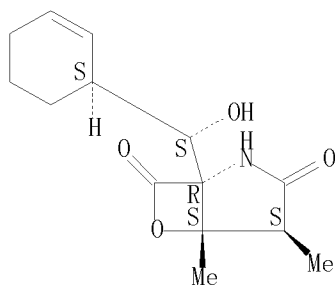
Absolute stereochemistry.



RN 872360-13-9 CAPLUS

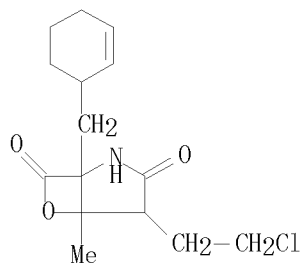
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4S,5S)-  
(CA INDEX NAME)

Absolute stereochemistry.



RN 872360-14-0 CAPLUS

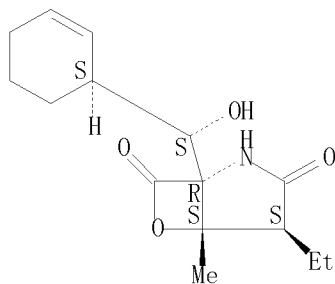
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-(2-cyclohexen-1-ylmethyl)-5-methyl-, (CA INDEX NAME)



RN 872360-16-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4S,5S)-  
(CA INDEX NAME)

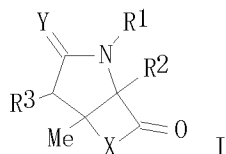
Absolute stereochemistry.





L6 ANSWER 141 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2006:1226095 CAPLUS  
 DOCUMENT NUMBER: 146:7751  
 TITLE: Synthesis of salinosporamide A and analogues thereof  
 INVENTOR(S): Danishefsky, Samuel; Endo, Atsushi  
 PATENT ASSIGNEE(S): Sloan-Kettering Institute for Cancer Research, USA  
 SOURCE: PCT Int. Appl., 127pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006124902	A2	20061123	WO 2006-US18924	20060516
WO 2006124902	A3	20061228		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20060287520	A1	20061221	US 2006-434698	20060516
PRIORITY APPLN. INFO.:			US 2005-681454P	P 20050516
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT				
OTHER SOURCE(S): CASREACT 146:7751; MARPAT 146:7751				
GRAPHIC IMAGE:				



# ABSTRACT:

A novel synthesis of salinosporamide A and compds. of formula I [X, Y = O, S, (substituted) CH, (substituted) NH; R1 = H, alkyl, cycloalkyl, etc.; R2 = CH(OH)R4; R3 = H, halo, alkyl, cycloalkyl, etc.; R4 = H, halo, alkyl, cycloalkyl, etc.] is provided. Salinosporamide A as well as structurally related natural products, omuralide and lactacystin, have been shown to be proteasome inhibitors. Therefore, these compds. as well as analogs of these natural products may be useful in the treatment of proliferative diseases such as cancer, autoimmune diseases, diabetic retinopathy, etc. The invention provides for the synthesis of salinosporamide A as well as analogs thereof using a convenient point for derivatization of the bicyclic core. Pharmaceutical compns. and method of using the inventive compds. are also provided.

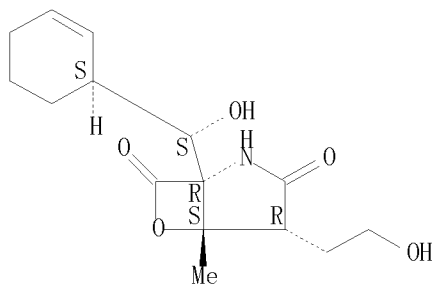
IT **823229-54-5P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (synthesis of salinosporamide A and analogs)

RN 823229-54-5 CAPLUS

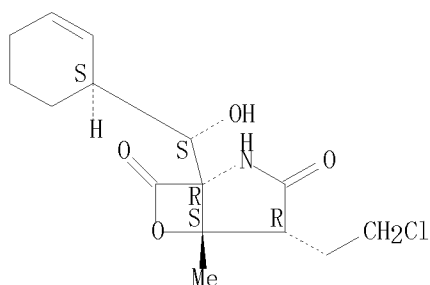
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **437742-34-2P**, Salinosporamide A  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (synthesis of salinosporamide A and analogs for the treatment of proliferative diseases)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

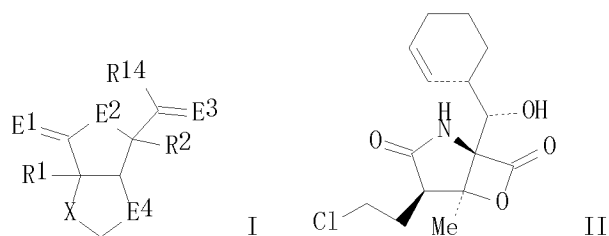


OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)  
 REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 142 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2006:1179912 CAPLUS  
DOCUMENT NUMBER: 145:487773  
TITLE: Methods of using salinosporamide and analogs thereof  
for treating cancer  
INVENTOR(S): Palladino, Michael; Potts, Barbara Christine;  
Macherla, Venkata Rami Reddy; Neuteboom, Saskia  
Theodora Cornelia  
PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
SOURCE: PCT Int. Appl., 251pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 5  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006118973	A2	20061109	WO 2006-US16104	20060427
WO 2006118973	A3	20070419		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			

PRIORITY APPLN. INFO.: US 2005-676533P P 20050429  
OTHER SOURCE(S): CASREACT 145:487773; MARPAT 145:487773  
GRAPHIC IMAGE:



#### ABSTRACT:

Title compds. I [X = (CH<sub>2</sub>)<sub>p</sub>; R1 = (un)substituted alkyl, alkenyl, alkynyl, acyl, etc.; R2 = H, halo, (un)substituted alkyl, alkoxy, etc.; R3 = halo, (un)substituted alkyl, alkenyl, acyloxy, etc.; R14 = halo, NO<sub>2</sub>, CN, etc.; p = 1-2; E1, E3 and E4 = (un)substituted heteroatom; E2 = (un)substituted heteroatom or CH<sub>2</sub>], and their pharmaceutically acceptable salts, are disclosed as useful for treating cancer. I are prepared via fermentation processes utilizing addnl. synthetic modifications to expand the scope of the analogs available. Numerous biol. assays are described, e.g., I were tested for inhibition of chymotrypsin-like activity of rabbit muscle proteasomes with salinosporamide A (II) demonstrating EC<sub>50</sub> value of 2.6 ± 0.2 nM.

#### IT 872360-11-7P

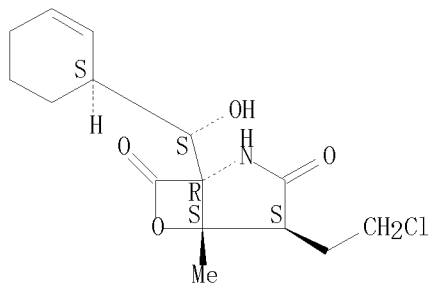
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(crystal structure; methods of using salinosporamide and analogs thereof derived via fermentation processes for treating cancer)

RN 872360-11-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,

(1R, 4S, 5S)- (CA INDEX NAME)

Absolute stereochemistry.

IT 823229-34-1P 872360-17-3P

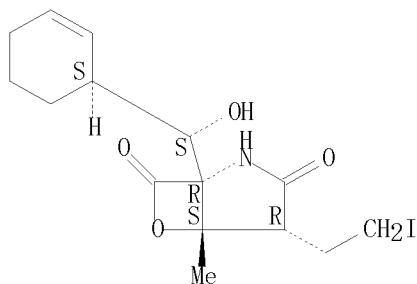
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(methods of using salinosporamide and analogs thereof derived via fermentation processes for treating cancer)

RN 823229-34-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

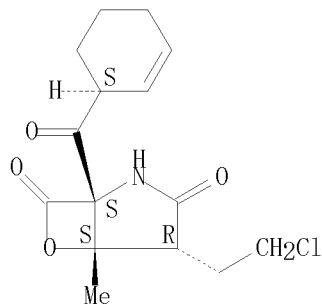
Absolute stereochemistry.



RN 872360-17-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
(1S, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.

IT 437742-34-2P 863126-95-8P 872360-15-1P

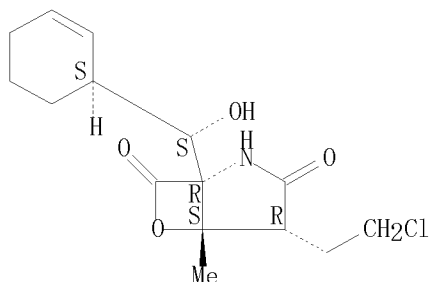
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(methods of using salinosporamide and analogs thereof derived via fermentation processes for treating cancer)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

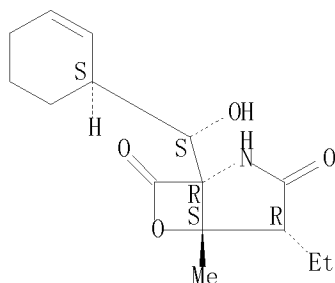
Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

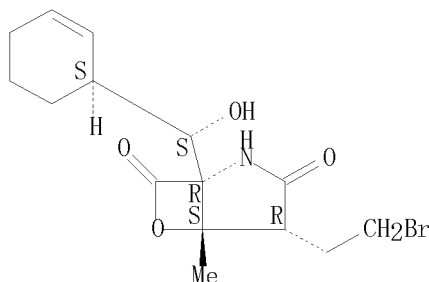
Absolute stereochemistry. Rotation (-).



RN 872360-15-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT	<u>823229-26-1P</u>	<u>823229-54-5P</u>	<u>823229-56-7P</u>
	<u>872360-12-8P</u>	<u>872360-13-9P</u>	<u>872360-14-0P</u>
	<u>872360-16-2P</u>	<u>872360-18-4P</u>	<u>872360-22-0P</u>
	<u>872360-23-1P</u>	<u>872360-24-2P</u>	

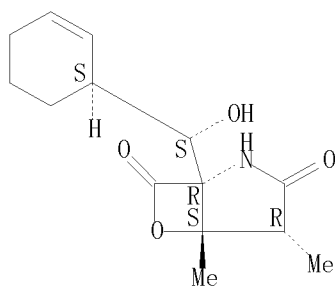
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(methods of using salinosporamide and analogs thereof derived via fermentation processes for treating cancer)

RN 823229-26-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4R,5S)-  
(CA INDEX NAME)



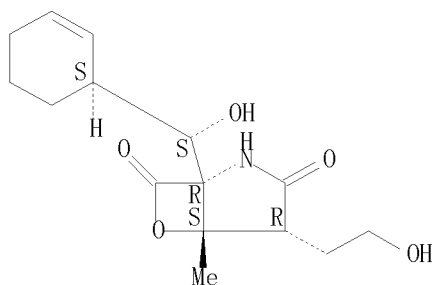
Absolute stereochemistry.



RN 823229-54-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

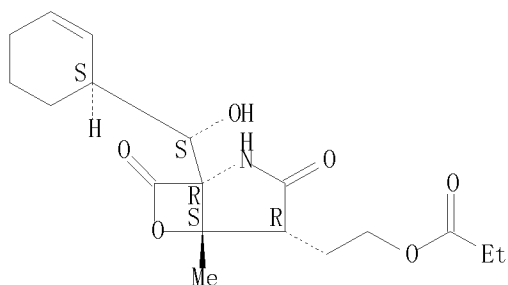
Absolute stereochemistry. Rotation (-).



RN 823229-56-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-, (1R, 4R, 5S)- (CA INDEX NAME)

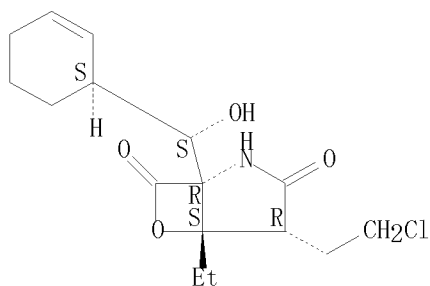
Absolute stereochemistry.



RN 872360-12-8 CAPLUS

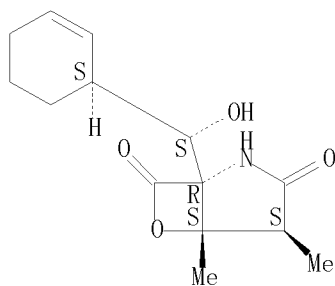
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-ethyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.

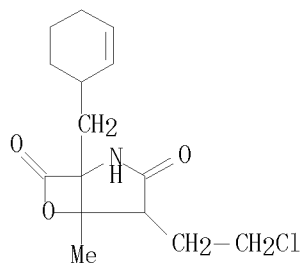


RN 872360-13-9 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4S,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.

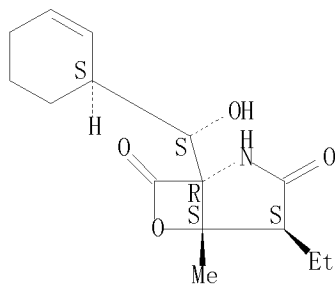


RN 872360-14-0 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-(2-cyclohexen-1-ylmethyl)-5-methyl- (CA INDEX NAME)



RN 872360-16-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4S,5S)-  
 (CA INDEX NAME)

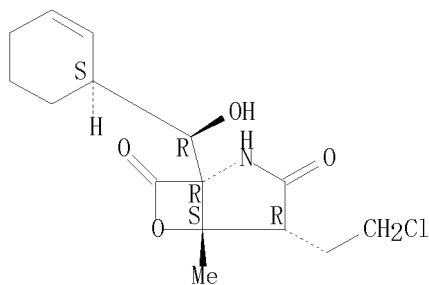
Absolute stereochemistry.



RN 872360-18-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

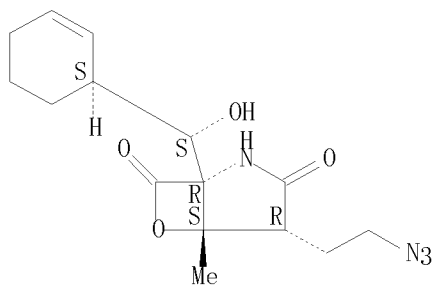
Absolute stereochemistry.



RN 872360-22-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-azidoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

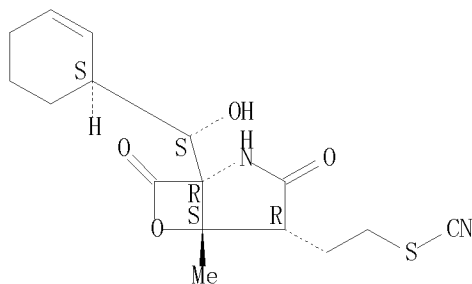
Absolute stereochemistry.



RN 872360-23-1 CAPLUS

CN Thiocyanic acid, 2-[(1R,4R,5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA INDEX NAME)

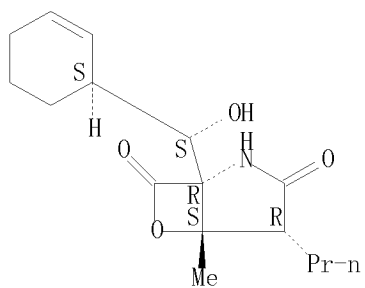
Absolute stereochemistry.



RN 872360-24-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

5

THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 143 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2006:1081796 CAPLUS  
DOCUMENT NUMBER: 146:154969  
TITLE: A novel proteasome inhibitor NPI-0052 as an anticancer therapy  
AUTHOR(S): Chauhan, D.; Hideshima, T.; Anderson, K. C.  
CORPORATE SOURCE: Department of Medical Oncology, The Jerome Lipper Multiple Myeloma Center, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115, USA  
SOURCE: British Journal of Cancer (2006), 95(8), 961-965  
CODEN: BJCAAI; ISSN: 0007-0920  
PUBLISHER: Nature Publishing Group  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
ABSTRACT:

A review. Proteasome inhibitor Bortezomib/Velcade has emerged as an effective anticancer therapy for the treatment of relapsed and/or refractory multiple myeloma (MM), but prolonged treatment can be associated with toxicity and development of drug resistance. In this review, we discuss the recent discovery of a novel proteasome inhibitor, NPI-0052, that is distinct from Bortezomib in its chemical structure, mechanisms of action, and effects on proteasomal activities; most importantly, it overcomes resistance to conventional and Bortezomib therapies. In vivo studies using human MM xenografts shows that NPI-0052 is well tolerated, prolongs survival, and reduces tumor recurrence. These preclin. studies provided the basis for Phase-I clin. trial of NPI-0052 in relapsed/refractory MM patients.

IT **437742-34-2**, NPI-0052

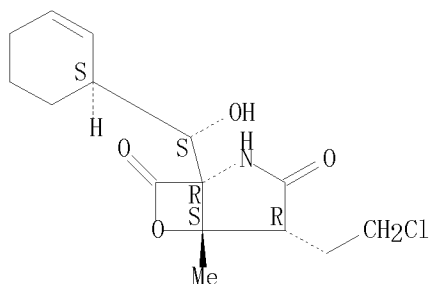
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(proteasome inhibitor, NPI-0052 as anticancer therapy for treatment of relapsed/refractory multiple myeloma)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 53 THERE ARE 53 CAPLUS RECORDS THAT CITE THIS RECORD (53 CITINGS)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 144 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2006:1006362 CAPLUS  
 DOCUMENT NUMBER: 145:369905  
 TITLE: Treatment of protein degradation disorders  
 INVENTOR(S): Anderson, Kenneth C.; Bradner, James Elliott;  
 Greenberg, Edward Franklin; Hideshima, Teru;  
 Kwiatkowski, Nicholas Paul; Mazitschek, Ralph;  
 Schreiber, Stuart L.; Shaw, Jared  
 PATENT ASSIGNEE(S): The President and Fellows of Harvard College, USA;  
 Dana-Farber Cancer Institute, Inc.  
 SOURCE: PCT Int. Appl., 194 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006102557	A2	20060928	WO 2006-US10676	20060322
WO 2006102557	A3	20090416		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
AU 2006226861	A1	20060928	AU 2006-226861	20060322
CA 2601706	A1	20060928	CA 2006-2601706	20060322
US 20060239909	A1	20061026	US 2006-386959	20060322
EP 1861126	A2	20071205	EP 2006-748614	20060322
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU			
JP 2009509910	T	20090312	JP 2008-503207	20060322
IN 2007KN04029	A	20080328	IN 2007-KN4029	20071018
CN 101495116	A	20090729	CN 2006-80017728	20071122
PRIORITY APPLN. INFO.:			US 2005-664470P	P 20050322
			WO 2006-US10676	W 20060322

# ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 145:369905

## ABSTRACT:

The invention relates to methods of treating protein degradation disorders, such cellular proliferative disorders (e.g., cancer) and protein deposition disorders (e.g., neurodegenerative disorders). The invention provides methods and pharmaceutical compns. for treating these diseases using aggresome inhibitors or combinations of aggresome inhibitors and proteasome inhibitors. The invention further relates to methods and pharmaceutical compns. for treating multiple myeloma. New HDAC (histone deacetylase)/TDAC (tubulin deacetylase) inhibitors and aggresome inhibitors are also provided as well as synthetic methodologies for preparing these compds.

IT **437742-34-2**, NPI-0052

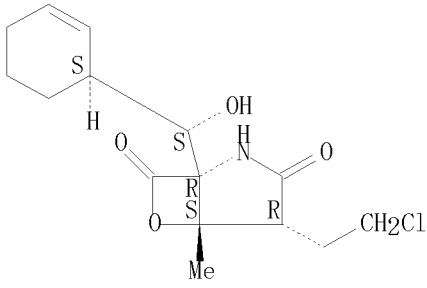
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(treatment of protein degradation disorders using protein degradation inhibitors in relation to cellular phenotype determination and screening and combination with other agents)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD  
(1 CITINGS)

L6 ANSWER 145 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2006:771737 CAPLUS  
DOCUMENT NUMBER: 145:241186  
TITLE: The proteasome inhibitor NPI-0052 is a more effective inducer of apoptosis than bortezomib in lymphocytes from patients with chronic lymphocytic leukemia  
AUTHOR(S): Ruiz, Stacey; Krupnik, Yelena; Keating, Michael; Chandra, Joya; Palladino, Michael; McConkey, David  
CORPORATE SOURCE: Department of Cancer Biology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030, USA  
SOURCE: Molecular Cancer Therapeutics (2006), 5(7), 1836-1843  
CODEN: MCTOCF; ISSN: 1535-7163  
PUBLISHER: American Association for Cancer Research  
DOCUMENT TYPE: Journal  
LANGUAGE: English

ABSTRACT:  
Proteasome inhibitors are potent inducers of apoptosis in isolated lymphocytes from patients with chronic lymphocytic leukemia (CLL). However, the reversible proteasome inhibitor bortezomib (PS-341; Velcade) did not display substantial antitumor activity in CLL patients. Here, we compared the effects of bortezomib and a new irreversible proteasome inhibitor (NPI-0052) on 20S chymotryptic proteasome activity and apoptosis in isolated CLL cells in vitro. Although their steady-state (3 h) IC50s as proteasome inhibitors were similar, NPI-0052 exerted its effects more rapidly than bortezomib, and drug washout expts. showed that short exposures to NPI-0052 resulted in sustained ( $\geq 24$  h) 20S proteasome inhibition, whereas 20S activity recovered in cells exposed to even 10-fold higher concns. of bortezomib. Thus, brief (15 min) pulses of NPI-0052 were sufficient to induce substantial apoptosis in CLL cells, whereas longer exposure times ( $\geq 8$  h) were required for commitment to apoptosis in cells exposed to equivalent concns. of bortezomib. Commitment to apoptosis seemed to be related to caspase-4 activation, in that cells exposed to bortezomib or NPI-0052 could be saved from death by addition of a selective caspase-4 inhibitor up to 8 h after drug exposure. Our results show that NPI-0052 is a more effective proapoptotic agent than bortezomib in isolated CLL cells and suggest that the chemical properties of NPI-0052 might also make it an effective therapeutic agent in CLL patients.

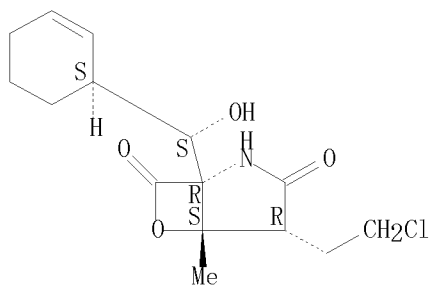
IT **437742-34-2**, NPI-0052

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(proteasome inhibitor NPI-0052 is a more effective inducer of apoptosis than bortezomib in lymphocytes from patients with chronic lymphocytic leukemia)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

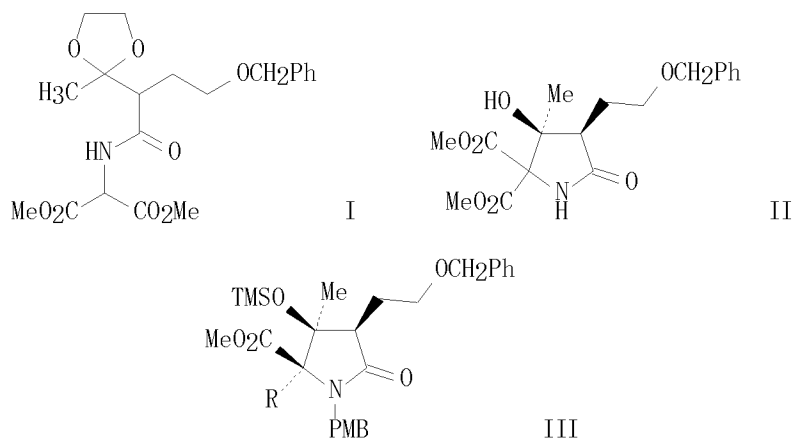
Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 50 THERE ARE 50 CAPLUS RECORDS THAT CITE THIS RECORD (51 CITINGS)  
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 146 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2006:718811 CAPLUS  
DOCUMENT NUMBER: 145:335821  
TITLE: A concise total synthesis of salinosporamide A  
AUTHOR(S): Mulholland, Nicholas P.; Pattenden, Gerald; Walters,  
Iain A. S.  
CORPORATE SOURCE: School of Chemistry, University of Nottingham,  
Nottingham, NG7 2RD, UK  
SOURCE: Organic & Biomolecular Chemistry (2006), 4(15),  
2845-2846  
CODEN: OBCRAK; ISSN: 1477-0520  
PUBLISHER: Royal Society of Chemistry  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
OTHER SOURCE(S): CASREACT 145:335821  
GRAPHIC IMAGE:



ABSTRACT:

A concise and straightforward 14-step total synthesis of ( $\pm$ )-salinosporamide A, based on a diastereoselective acid-catalyzed intramol. cyclization of I to the pyrrolidinone II, and a regioselective reduction of the malonate derivative III (R = CO<sub>2</sub>Me) to the aldehyde III (R = CHO), is described.

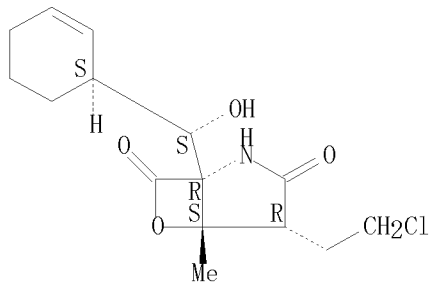
## IT 909569-43-3P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(stereoselective synthesis of salinosporamide A via diastereoselective acid-catalyzed intramol. cyclization to a pyrrolidinone and regioselective reduction of a malonate)

RN 909569-43-3 CAPLUS

CN 6-0xa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1R)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1S,4S,5R)-rel- (CA INDEX NAME)

Relative stereochemistry.



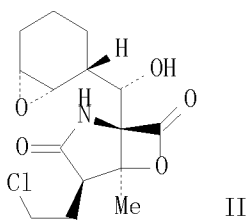
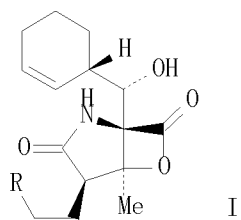
OS.CITING REF COUNT:	30	THERE ARE 30 CAPLUS RECORDS THAT CITE THIS RECORD (32 CITINGS)
REFERENCE COUNT:	27	THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 147 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2006:544606 CAPLUS  
DOCUMENT NUMBER: 145:45846  
TITLE: Preparation of salinosporamide A and analogous [3.2.0]  
bicyclic  $\beta$ -lactones for use in anti-cancer  
pharmaceutical compositions  
INVENTOR(S): Palladino, Michael; Potts, Barbara Christine;  
Macherla, Venkata Rami Reddy; Neuteboom, Saskia  
Theodora Cornelia  
PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
SOURCE: PCT Int. Appl., 282 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 5  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006060809	A2	20060608	WO 2005-US44091	20051202
WO 2006060809	A3	20061005		
WO 2006060809	A9	20080117		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
AU 2005311572	A1	20060608	AU 2005-311572	20051202
CA 2590334	A1	20060608	CA 2005-2590334	20051202
EP 1835910	A2	20070926	EP 2005-853102	20051202
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR			
JP 2008522975	T	20080703	JP 2007-544616	20051202
ZA 2007004461	A	20100825	ZA 2007-4461	20070530
MX 2007006523	A	20070911	MX 2007-6523	20070531
KR 2007086895	A	20070827	KR 2007-7015201	20070702
CN 101208087	A	20080625	CN 2005-80047746	20070803
PRIORITY APPLN. INFO.:			US 2004-633379P	P 20041203
			US 2005-643922P	P 20050113
			US 2005-658884P	P 20050304
			US 2005-676533P	P 20050429
			WO 2005-US44091	W 20051202

OTHER SOURCE(S): MARPAT 145:45846  
GRAPHIC IMAGE:



#### ABSTRACT:

Salinosporamide A I (R = Cl) and its analogs were prepared for therapeutic use in the treatment of cancer, inflammatory conditions, and/or infectious disease. I was prepared via a fermentation process using strain CNB476 or strain NPS21184. I and related bicyclic  $\beta$ -lactones recovered from the fermentation process were subsequently converted to other  $\beta$ -lactone derivs., such as I (R = H, Br, iodo, Me) and II. The prepared  $\beta$ -lactones were extensively tested for anticancer, anti-inflammatory and antibacterial activity.

IT **823229-34-1P** **872360-17-3P**

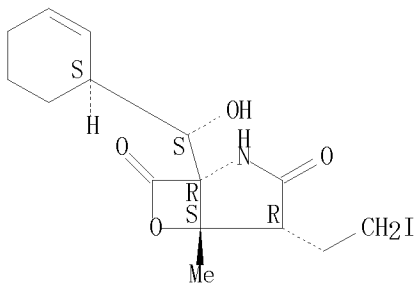
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of salinosporamide A and analogous [3.2.0] bicyclic  $\beta$ -lactones for use in anti-cancer pharmaceutical compns.)

RN 823229-34-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

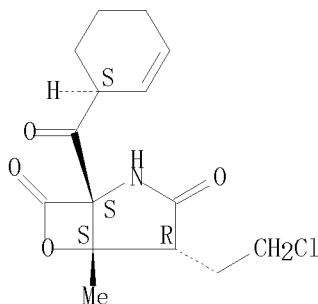
Absolute stereochemistry.



RN 872360-17-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
(1S,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

IT **437742-34-2P**, Salinosporamide A **863126-95-8P****872360-15-1P**

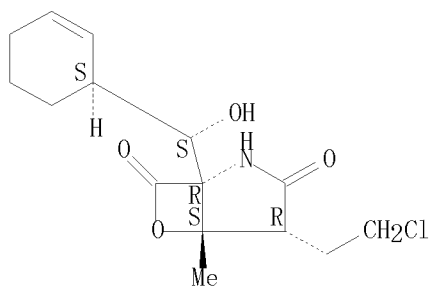
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of salinosporamide A and analogous [3.2.0] bicyclic  $\beta$ -lactones for use in anti-cancer pharmaceutical compns.)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

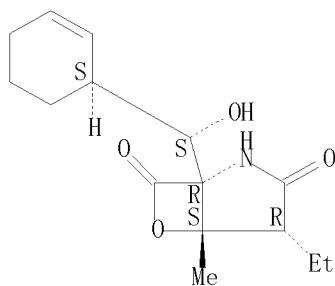
Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R, 4R, 5S)-  
(CA INDEX NAME)

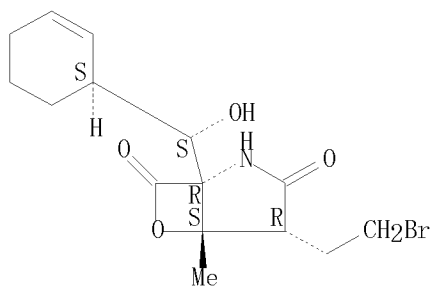
Absolute stereochemistry. Rotation (-).



RN 872360-15-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 823229-54-5P 823229-56-7P 872360-18-4P  
872360-22-0P 872360-23-1P 872360-24-2P

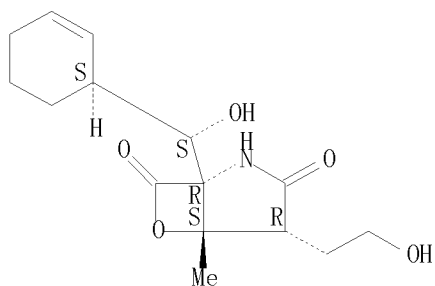
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN  
(Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);  
PREP (Preparation); USES (Uses)

(preparation of salinosporamide A and analogous [3.2.0] bicyclic  
β-lactones for use in anti-cancer pharmaceutical compns.)

RN 823229-54-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

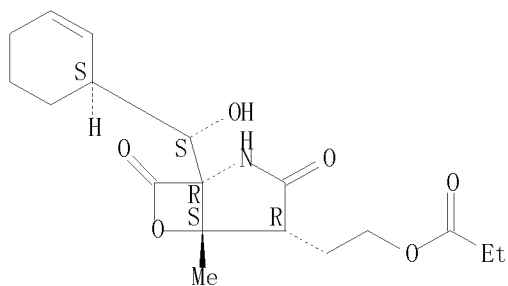
Absolute stereochemistry. Rotation (-).



RN 823229-56-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

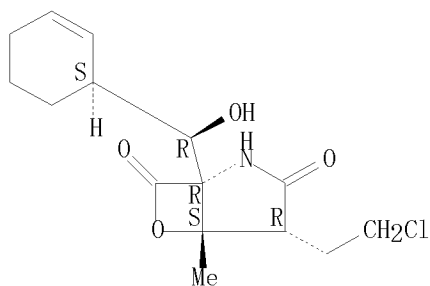
Absolute stereochemistry.



RN 872360-18-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

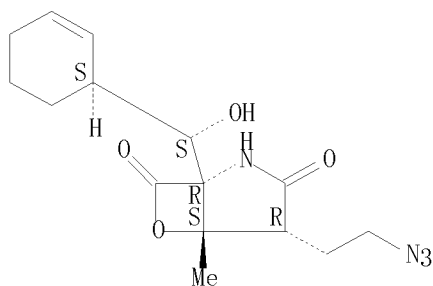
Absolute stereochemistry.



RN 872360-22-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-azidoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

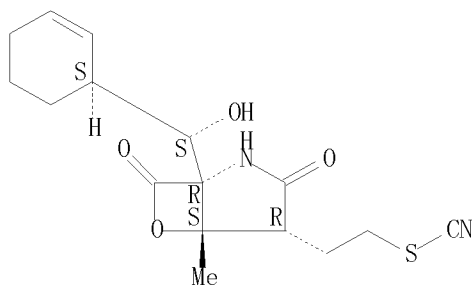
Absolute stereochemistry.



RN 872360-23-1 CAPLUS

CN Thiocyanic acid, 2-[(1R, 4R, 5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA INDEX NAME)

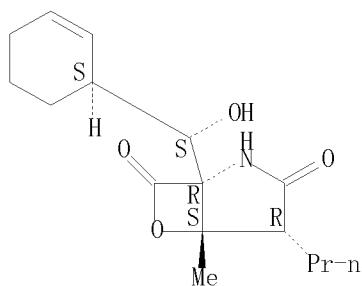
Absolute stereochemistry.



RN 872360-24-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-, (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 823229-26-1P 872360-11-7P 872360-12-8P  
872360-13-9P 872360-14-0P 872360-16-2P

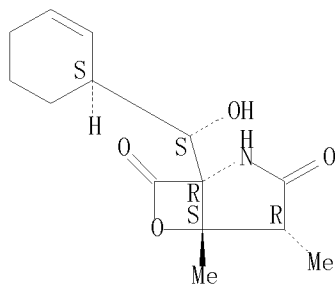
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of salinosporamide A and analogous [3.2.0] bicyclic  $\beta$ -lactones for use in anti-cancer pharmaceutical compns.)

RN 823229-26-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R, 4R, 5S)- (CA INDEX NAME)

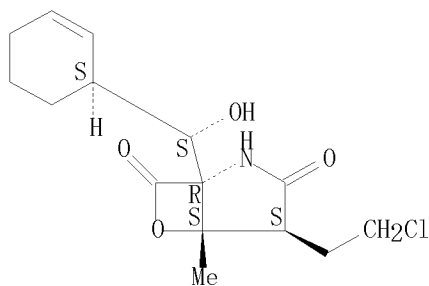
Absolute stereochemistry.



RN 872360-11-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4S,5S)- (CA INDEX NAME)

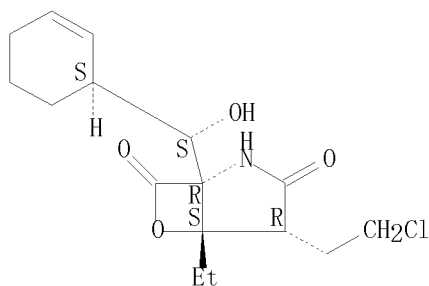
Absolute stereochemistry.



RN 872360-12-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-ethyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

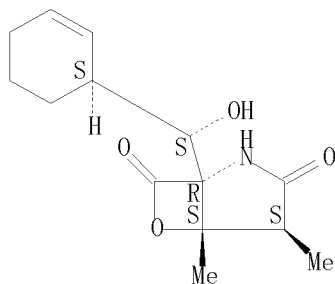


RN 872360-13-9 CAPLUS

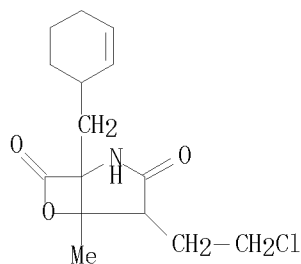
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4S,5S)-  
(CA INDEX NAME)

Absolute stereochemistry.



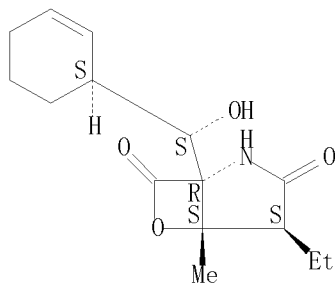


RN 872360-14-0 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-(2-cyclohexen-1-ylmethyl)-5-methyl- (CA INDEX NAME)



RN 872360-16-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4S,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD  
 (4 CITINGS)  
 REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 148 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2006:542726 CAPLUS  
DOCUMENT NUMBER: 145:40243  
TITLE: Dehydroxymethylepoxyquinomicin (DHMEQ) as a  
sensitizing agent for therapy of resistant cancer  
cells  
INVENTOR(S): Bonavida, Benjamin  
PATENT ASSIGNEE(S): The Regents of the University of California, USA  
SOURCE: PCT Int. Appl., 61 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006060819	A2	20060608	WO 2005-US44170	20051205
WO 2006060819	A3	20070920		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			

PRIORITY APPLN. INFO.: US 2004-632900P P 20041203

OTHER SOURCE(S): MARPAT 145:40243

ABSTRACT:

The invention identifies DHMEQ as a sensitizing agent for therapy (e.g., chemotherapy, hormonal therapy, radiotherapy and immunotherapy) of resistant and sensitive cells. The invention provides methods for treating drug- and immunotherapy-sensitive cancers and treating drug- and immunotherapy-resistant cancers with DHMEQ or structurally similar compds. either alone or in combination with chemotherapy, hormonal therapy, radiotherapy and immunotherapy agents. Compound preparation is described.

IT **437742-34-2**, Salinosporamide A

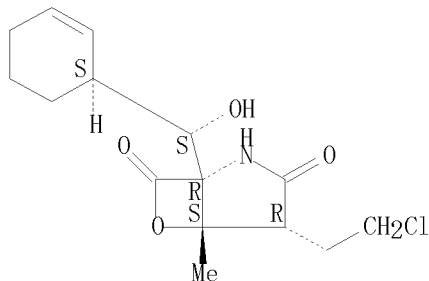
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(dehydroxymethylepoxyquinomicin as sensitizing agent for therapy of resistant cancer cells)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD  
(2 CITINGS)

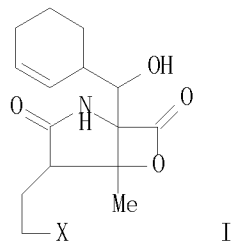
L6 ANSWER 149 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2006:542206 CAPLUS  
 DOCUMENT NUMBER: 145:21145  
 TITLE: Proteasome inhibitors and methods for treating  
 neoplastic diseases  
 INVENTOR(S): Anderson, Kenneth, C.; Chauhan, Dharminder  
 PATENT ASSIGNEE(S): Dana Farber Cancer Institute, USA  
 SOURCE: PCT Int. Appl., 81 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006060676	A1	20060608	WO 2005-US43668	20051202
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2005311709	A1	20060608	AU 2005-311709	20051202
CA 2588923	A1	20060608	CA 2005-2588923	20051202
EP 1830838	A1	20070912	EP 2005-852783	20051202
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
US 20070225350	A1	20070927	US 2005-293354	20051202
JP 2008521928	T	20080626	JP 2007-544545	20051202
BR 2005017135	A	20080930	BR 2005-17135	20051202
SG 157365	A1	20091229	SG 2009-7327	20051202
NZ 555439	A	20101224	NZ 2005-555439	20051202
ZA 2007004402	A	20080730	ZA 2007-4402	20070529
MX 2007006526	A	20070919	MX 2007-6526	20070531
KR 2008003306	A	20080107	KR 2007-7015299	20070703
CN 101155582	A	20080402	CN 2005-80046615	20070713
US 20090036390	A1	20090205	US 2008-183007	20080730
PRIORITY APPLN. INFO.:			US 2004-633161P	P 20041203
			US 2005-293354	B1 20051202
			WO 2005-US43668	W 20051202

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 145:21145

GRAPHIC IMAGE:



#### ABSTRACT:

Disclosed herein are compns. and methods for treating neoplastic diseases, e.g., effective against multiple myeloma cells resistant to conventional and bortezomib treatment. The compns. comprise a compound of formula (I) (X = Br, Cl, F, I). Furthermore, combination treatment with two different proteasome inhibitors is shown to be synergistic for treating multiple myeloma. Thus, NPI 0052 inhibited in a dose-dependent manner chymotrypsin-like activity of 20S proteasome in whole blood cells of mice after a single i.v. or oral

administration. Also, NPI 0052 induced apoptosis in human multiple myeloma (MM) cells sensitive and resistant to conventional and bortezomib therapies. The IC<sub>50</sub> of the compound for MM cells was within the nanomolar concentration

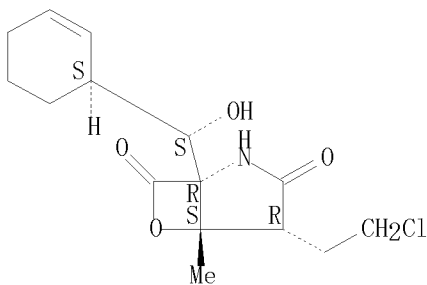
IT 437742-34-2, NPI 0052 823229-08-9  
823229-10-3      823229-12-5      823229-14-7  
823229-34-1      872360-15-1      889457-14-1

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (proteasome inhibitors and other antitumor agents for treating neoplastic diseases)

RN 437742-34-2 CAPLUS

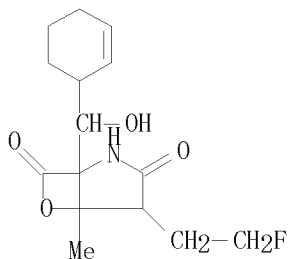
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



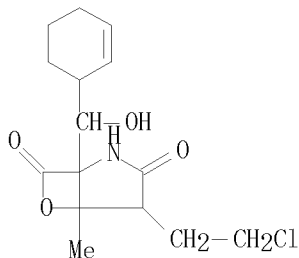
RN 823229-08-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-(2-cyclohexen-1-ylhydroxymethyl)-4-(2-fluoroethyl)-5-methyl- (CA INDEX NAME)



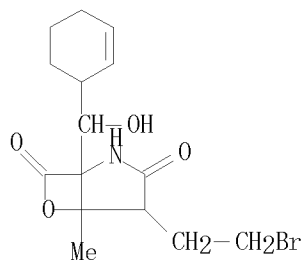
RN 823229-10-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-(2-cyclohexen-1-ylhydroxymethyl)-5-methyl- (CA INDEX NAME)



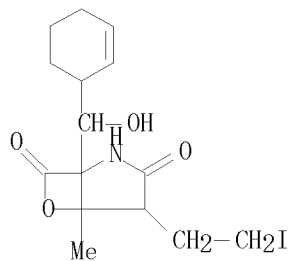
RN 823229-12-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-bromoethyl)-1-(2-cyclohexen-1-ylhydroxymethyl)-5-methyl- (CA INDEX NAME)



RN 823229-14-7 CAPLUS

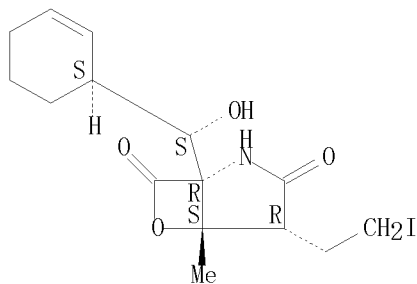
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(2-cyclohexen-1-ylhydroxymethyl)-4-(2-iodoethyl)-5-methyl- (CA INDEX  
NAME)



RN 823229-34-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

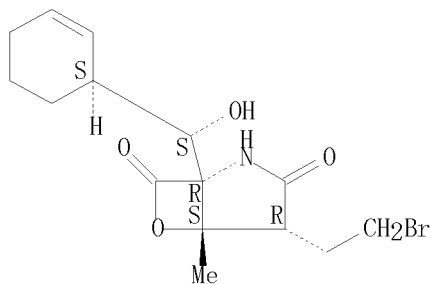
Absolute stereochemistry.



RN 872360-15-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

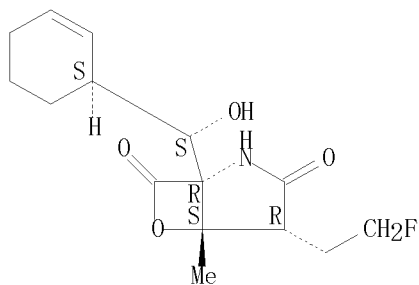
Absolute stereochemistry.



RN 889457-14-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-fluoroethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



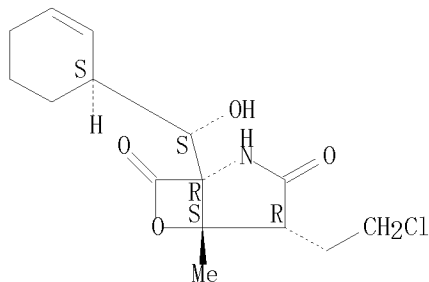
OS.CITING REF COUNT:	3	THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT:	6	THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 150 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2006:529516 CAPLUS  
DOCUMENT NUMBER: 145:188596  
TITLE: Studies toward the synthesis of salinosporamide A, a  
potent proteasome inhibitor  
AUTHOR(S): Caubert, Virginie; Langlois, Nicole  
CORPORATE SOURCE: Institut de Chimie des Substances Naturelles, CNRS,  
Gif-sur-Yvette, 91198, Fr.  
SOURCE: Tetrahedron Letters (2006), 47(26), 4473-4475  
CODEN: TELEAY; ISSN: 0040-4039  
PUBLISHER: Elsevier B.V.  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
OTHER SOURCE(S): CASREACT 145:188596  
ABSTRACT:

An  $\alpha$ -methylenepyrrolidinone bearing all the functionalities and relative configurations of an advanced intermediate in the synthesis of salinosporamide A and analogs was synthesized from Me pyroglutamate through regio- and stereoselective N-methylnitrone cycloaddn.

IT 437742-34-2P, Salinosporamide A  
RL: PNU (Preparation, unclassified); PREP (Preparation)  
(preparation of methylenepyrrolidinone as salinosporamide A precursor from  
pyroglutamate by regio- and stereoselective nitrone cycloaddn.)  
RN 437742-34-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



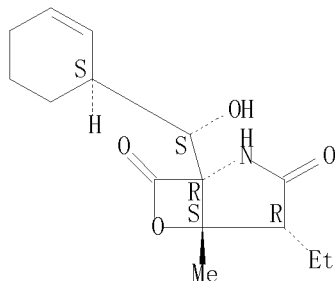
OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS  
RECORD (16 CITINGS)  
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 151 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2006:277393 CAPLUS  
 DOCUMENT NUMBER: 144:365306  
 TITLE: Crystal Structures of Salinosporamide A (NPI-0052) and B (NPI-0047) in Complex with the 20S Proteasome Reveal Important Consequences of  $\beta$ -Lactone Ring Opening and a Mechanism for Irreversible Binding  
 AUTHOR(S): Groll, Michael; Huber, Robert; Potts, Barbara C. M.  
 CORPORATE SOURCE: Ludwig-Maximilians-University of Munich, Munich, 81377, Germany  
 SOURCE: Journal of the American Chemical Society (2006), 128(15), 5136-5141  
 CODEN: JACSAT; ISSN: 0002-7863  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 ABSTRACT:

The crystal structures of the yeast 20S proteasome core particle (CP) in complex with Salinosporamides A (NPI-0052; 1) and B (4) were solved at  $<3$  Å resolution. Each ligand is covalently bound to Thr10 $\gamma$  via an ester linkage to the carbonyl derived from the  $\beta$ -lactone ring of the inhibitor. In the case of 1, nucleophilic addition to the  $\beta$ -lactone ring is followed by addition of C-30 to the chloroethyl group, giving rise to a cyclic ether. The crystal structures were compared to that of the omuralide/CP structure solved previously, and the collective data provide new insights into the mechanism of inhibition and irreversible binding of 1. Upon opening of the  $\beta$ -lactone ring, C-30 assumes the position occupied by a water mol. in the unligated enzyme and hinders deacylation of the enzyme-ligand complex. Furthermore, the resulting protonation state of Thr1NH2 deactivates the catalytic N-terminus.

IT **863126-95-8D**, Salinosporamide B, complexes with 20S proteasome  
 RL: PRP (Properties)  
 (NPI 0047; crystal structures of salinosporamides A and B in complex with 20S proteasome address mol. basis of Thr1-associated  $\beta$ -lactone ring opening and irreversible binding)  
 RN 863126-95-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

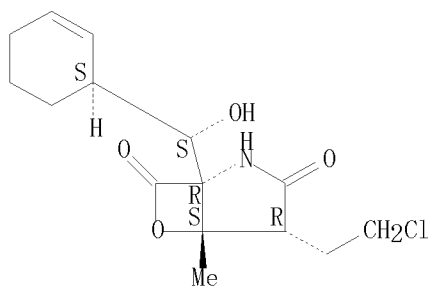
Absolute stereochemistry. Rotation (-).



IT **437742-34-2D**, Salinosporamide A, complexes with 20S proteasome  
 RL: PRP (Properties)  
 (crystal structures of salinosporamides A and B in complex with 20S proteasome address mol. basis of Thr1-associated  $\beta$ -lactone ring opening and irreversible binding)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

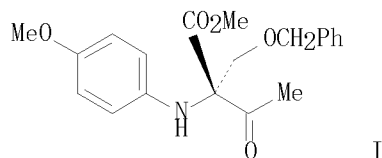
Absolute stereochemistry. Rotation (-).





OS.CITING REF COUNT:	96	THERE ARE 96 CAPLUS RECORDS THAT CITE THIS RECORD (97 CITINGS)
REFERENCE COUNT:	30	THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 152 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2006:274086 CAPLUS  
 DOCUMENT NUMBER: 145:7903  
 TITLE: Novel Bicyclization Reaction Leading to a Fused  $\beta$ -Lactone  
 AUTHOR(S): Reddy, Leleti Rajender; Corey, E. J.  
 CORPORATE SOURCE: Harvard University, Cambridge, MA, 02138, USA  
 SOURCE: Organic Letters (2006), 8(8), 1717-1719  
 CODEN: ORLEF7; ISSN: 1523-7060  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 145:7903  
 GRAPHIC IMAGE:



## ABSTRACT:

The reaction of acryloyl chloride with the amino ketone I in the presence of pyridine produces bicyclic  $\beta$ -lactones rather than the corresponding acrylamide, which can be the major product under other conditions and which is an intermediate for the synthesis of salinosporamide A.

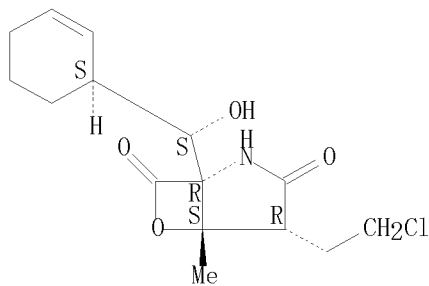
IT **437742-34-2P**, Salinosporamide A

RL: PNU (Preparation, unclassified); PREP (Preparation)  
 (novel bicyclization reaction leading to a fused  $\beta$ -lactone)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS  
 RECORD (10 CITINGS)  
 REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

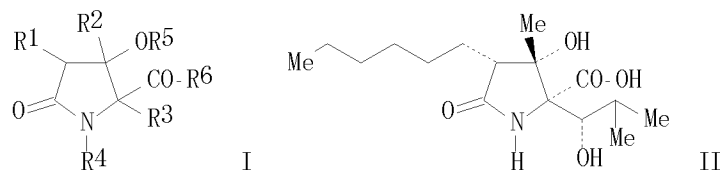
L6 ANSWER 153 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 2006:54100 CAPLUS  
DOCUMENT NUMBER: 144:128796  
TITLE: Preparation of substituted 2-pyrrolidone derivatives  
for use as agrochemical fungicides and insecticides  
INVENTOR(S): Hillebrand, Stefan; Guth, Oliver; Wiese,  
Welf-Burkhard; Kunz, Klaus; Ullmann, Astrid; Mattes,  
Amos; Schreier, Peter; Wachendorff-Neumann, Ulrike;  
Kuck, Karl-Heinz; Loesel, Peter; Malsam, Olga;  
Reinemer, Peter; Stadler, Marc; Seip, Stephan;  
Mayer-Bartschmid, Anke; Mueller, Hartwig; Bacon, Kevin  
PATENT ASSIGNEE(S): Bayer Cropscience A.-G., Germany  
SOURCE: PCT Int. Appl., 303 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006005551	A1	20060119	WO 2005-EP7442	20050709
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
EP 1771411	A1	20070411	EP 2005-761529	20050709
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR			
JP 2008505956	T	20080228	JP 2007-520728	20050709
BR 2005013262	A	20080429	BR 2005-13262	20050709
MX 2007000392	A	20070615	MX 2007-392	20070110
IN 2007DN00261	A	20070803	IN 2007-DN261	20070110
ZA 2007000278	A	20071128	ZA 2007-278	20070110
KR 2007041742	A	20070419	KR 2007-7003084	20070208
CN 101133022	A	20080227	CN 2005-80030203	20070308
US 20080064736	A1	20080313	US 2007-572086	20070720
PRIORITY APPLN. INFO.:			EP 2004-16320	A 20040712
			WO 2005-EP7442	W 20050709

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 144:128796; MARPAT 144:128796

GRAPHIC IMAGE:



#### ABSTRACT:

2-Pyrrolidone derivs., such as I [R1 = H, halogen, alkyl, alkenyl, alkynyl aryl, heterocyclyl, cycloalkyl, etc.; R2 = H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl; R3 = H, alkyl, alkenyl, alkynyl, etc.; R4 = H, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, etc.; R5 = H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl; R6 = OR, SR, NRR'; R, R' = H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl; R5R6 = bond], were prepared for use as argochems. for the control of insects and phytopathogenic plant fungi. Thus, 4R-hexyl-3S-hydroxy-2R-(1S-hydroxy-2-methylpropyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid (II) via a multistep synthesis starting from Me 5S-isopropyl-2-phenyl-4,5-dihydro-1,3-oxazole-4R-

carboxylate and Me 2-acetyloctanoate. The prepared pyrrolidones were tested for activity against *Podosphaera leucotricha*, *Venturia inaequalis*, *Botrytis cinerea*, *Phytophthora infestans*, and *Spodoptera frugiperda*.

IT	<u>223246-07-9</u>	<u>1044998-84-6</u>	<u>1044998-85-7</u>
	<u>1044998-86-8</u>	<u>1044998-93-7</u>	<u>1044998-94-8</u>
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	<u>1045004-69-0</u>	<u>1045004-70-3</u>	<u>1045004-71-4</u>
	<u>1045004-72-5</u>	<u>1045004-81-6</u>	<u>1045004-82-7</u>
	<u>1045004-83-8</u>	<u>1045004-84-9</u>	<u>1045004-90-7</u>
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	<u>1045008-38-5</u>	<u>1045008-39-6</u>	<u>1045008-40-9</u>
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	<u>1045008-49-8</u>	<u>1045008-50-1</u>	<u>1045008-51-2</u>
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	<u>1045008-84-1</u>	<u>1045008-90-9</u>	<u>1045008-91-0</u>
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	<u>1071908-05-8</u>	<u>1071955-02-6</u>	<u>1071955-11-7</u>
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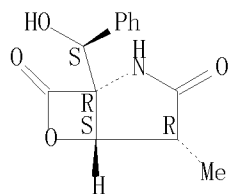
RL: PRPH (Prophetic)

(Preparation of substituted 2-pyrrolidone derivatives for use as agrochemical fungicides and insecticides)

RN 223246-07-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-4-methyl-, (1R,4R,5S)- (CA INDEX NAME)

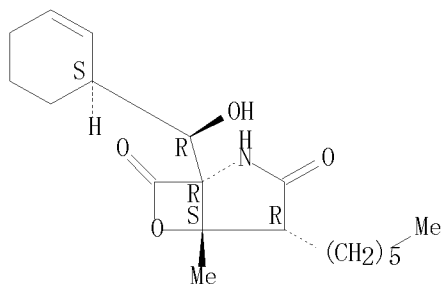
Absolute stereochemistry.



RN 1044998-84-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

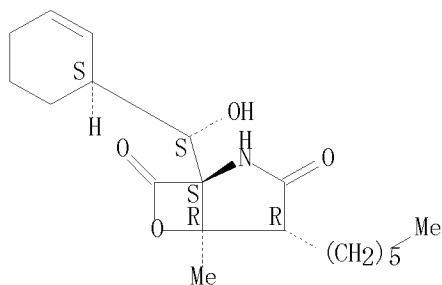
Absolute stereochemistry.



RN 1044998-85-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-, (1S,4R,5R)-  
(CA INDEX NAME)

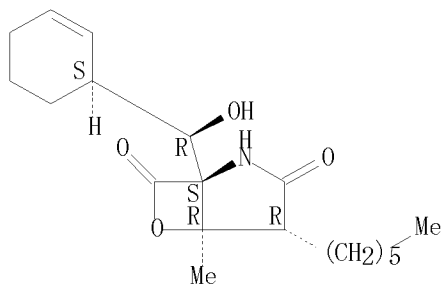
Absolute stereochemistry.



RN 1044998-86-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-, (1S,4R,5R)-  
(CA INDEX NAME)

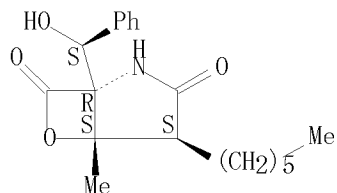
Absolute stereochemistry.



RN 1044998-93-7 CAPLUS

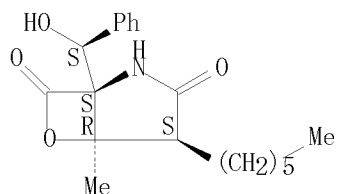
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



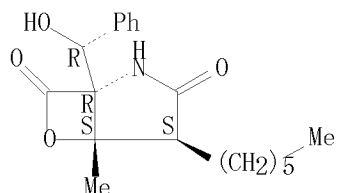
RN 1044998-94-8 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



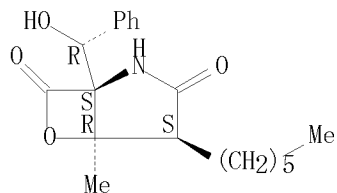
RN 1044998-95-9 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



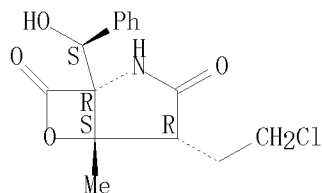
RN 1044998-96-0 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



RN 1044999-00-9 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA  
INDEX NAME)

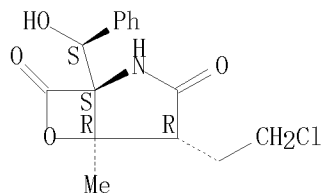
Absolute stereochemistry.



RN 1044999-01-0 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,

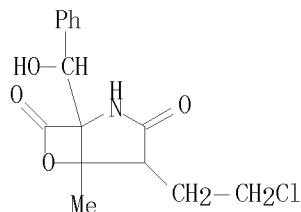
4-(2-chloroethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1S, 4R, 5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1044999-02-1 CAPLUS

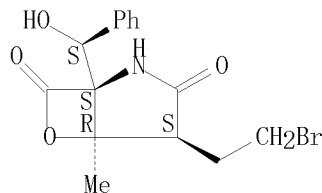
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-(hydroxyphenylmethyl)-5-methyl- (CA INDEX NAME)



RN 1044999-06-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1S, 4S, 5R)- (CA INDEX NAME)

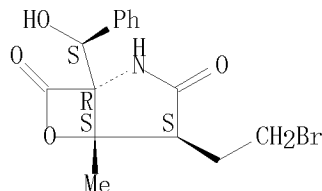
Absolute stereochemistry.



RN 1044999-08-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R, 4S, 5S)- (CA INDEX NAME)

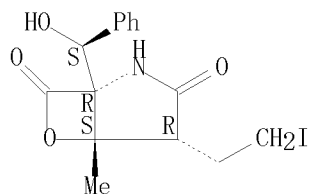
Absolute stereochemistry.



RN 1044999-11-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-4-(2-iodoethyl)-5-methyl-, (1R, 4R, 5S)- (CA INDEX NAME)

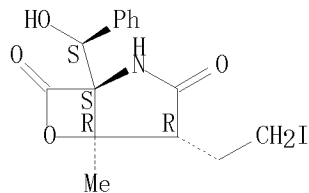
Absolute stereochemistry.



RN 1044999-13-4 CAPLUS

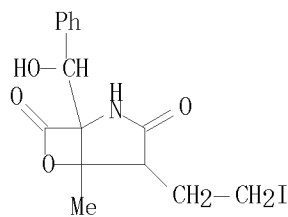
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-4-(2-iodoethyl)-5-methyl-, (1S,4R,5R)- (CA  
INDEX NAME)

Absolute stereochemistry.



RN 1044999-14-5 CAPLUS

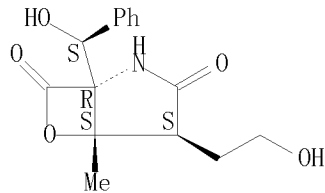
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(hydroxyphenylmethyl)-4-(2-iodoethyl)-5-methyl- (CA INDEX NAME)



RN 1044999-19-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-hydroxyethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4S,5S)- (CA  
INDEX NAME)

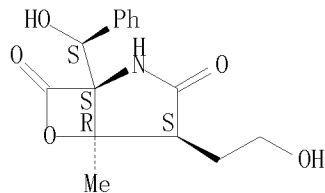
Absolute stereochemistry.



RN 1044999-21-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-hydroxyethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1S,4S,5R)- (CA  
INDEX NAME)

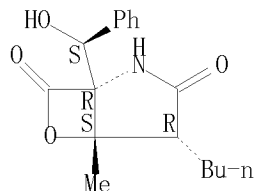
Absolute stereochemistry.





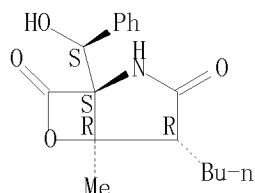
RN 1044999-25-8 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

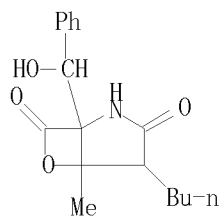


RN 1044999-26-9 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

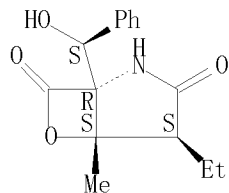


RN 1044999-27-0 CAPLUS  
CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-butyl-1-(hydroxyphenylmethyl)-5-methyl- (CA INDEX NAME)



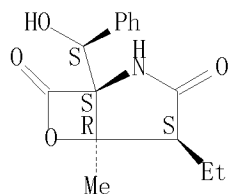
RN 1044999-31-6 CAPLUS  
CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-ethyl-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1044999-33-8 CAPLUS  
CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-ethyl-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1S,4S,5R)- (CA INDEX NAME)

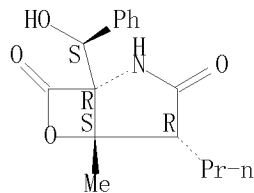
Absolute stereochemistry.



RN 1044999-35-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-5-methyl-4-propyl-, (1R, 4R, 5S)- (CA INDEX NAME)

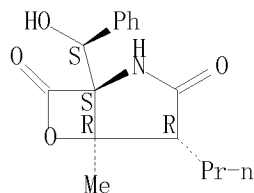
Absolute stereochemistry.



RN 1044999-38-3 CAPLUS

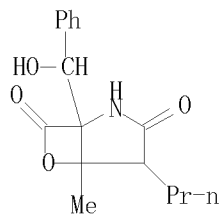
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-5-methyl-4-propyl-, (1S, 4R, 5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1044999-39-4 CAPLUS

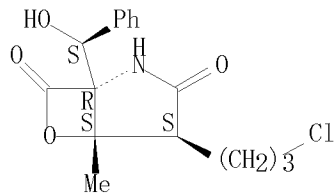
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(hydroxyphenylmethyl)-5-methyl-4-propyl- (CA INDEX NAME)



RN 1044999-44-1 CAPLUS

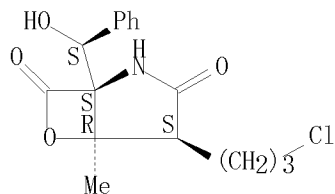
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(3-chloropropyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R, 4S, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



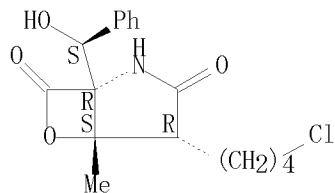
RN 1044999-45-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(3-chloropropyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1S,4S,5R)- (CA  
 INDEX NAME)

Absolute stereochemistry.



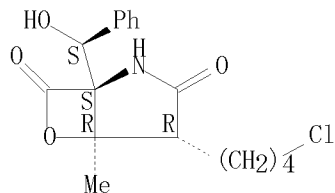
RN 1044999-50-9 CAPLUS  
 CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



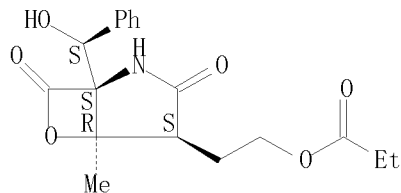
RN 1044999-51-0 CAPLUS  
 CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



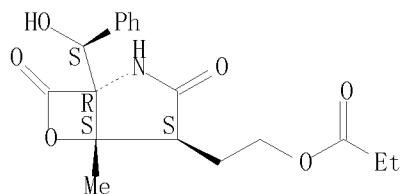
RN 1044999-56-5 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-hydroxyphenylmethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-,  
 (1S,4S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1044999-57-6 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-hydroxyphenylmethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-,  
 (1R,4S,5S)- (CA INDEX NAME)

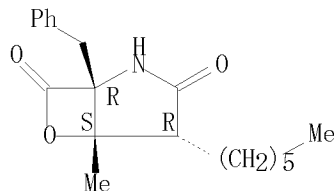
Absolute stereochemistry.



RN 1044999-62-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-hexyl-5-methyl-1-(phenylmethyl)-, (1R,4R,5S)- (CA INDEX NAME)

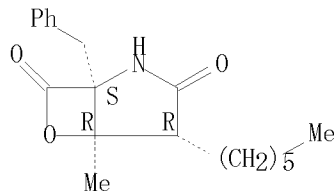
Absolute stereochemistry.



RN 1044999-64-5 CAPLUS

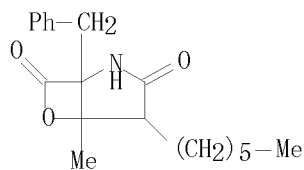
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-hexyl-5-methyl-1-(phenylmethyl)-, (1S,4R,5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1044999-65-6 CAPLUS

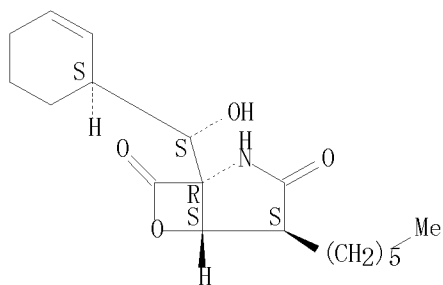
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-hexyl-5-methyl-1-(phenylmethyl)- (CA INDEX NAME)



RN 1044999-66-7 CAPLUS

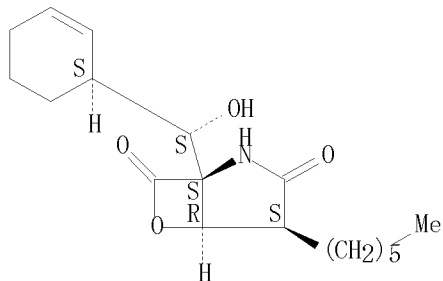
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-, (1R,4S,5S)- (CA  
INDEX NAME)

Absolute stereochemistry.



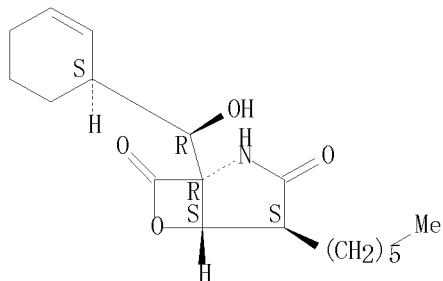
RN 1044999-67-8 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-, (1S,4S,5R)- (CA  
INDEX NAME)

Absolute stereochemistry.



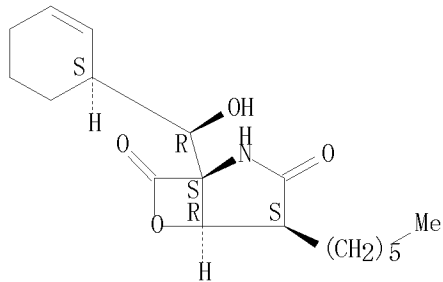
RN 1044999-68-9 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-, (1R,4S,5S)- (CA  
INDEX NAME)

Absolute stereochemistry.



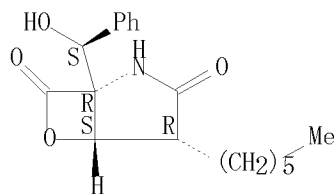
RN 1044999-69-0 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-, (1S,4S,5R)- (CA  
INDEX NAME)

Absolute stereochemistry.



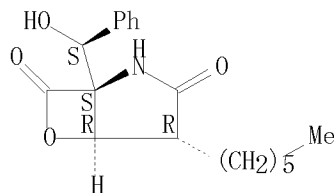
RN 1044999-78-1 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



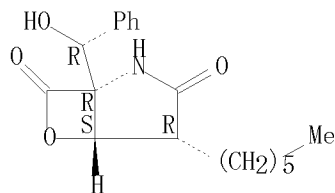
RN 1044999-79-2 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



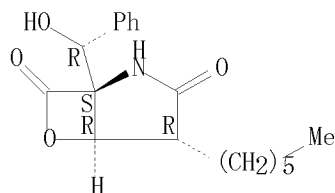
RN 1044999-80-5 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

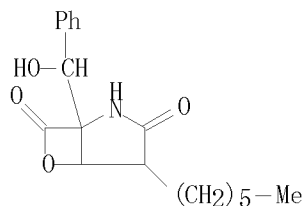


RN 1044999-81-6 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

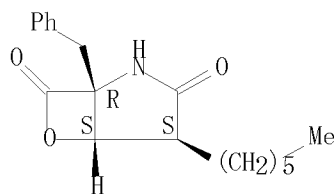


RN 1044999-82-7 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-hexyl-1-(hydroxyphenylmethyl)- (CA INDEX NAME)



RN 1044999-88-3 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-hexyl-1-(phenylmethyl)-,  
(1R,4S,5S)- (CA INDEX NAME)

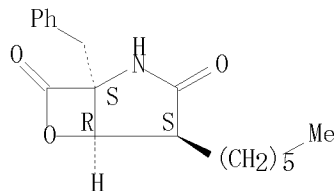
Absolute stereochemistry.



RN 1045000-71-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-hexyl-1-(phenylmethyl)-,  
(1S,4S,5R)- (CA INDEX NAME)

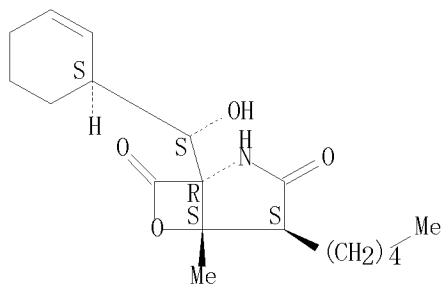
Absolute stereochemistry.



RN 1045000-72-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-pentyl-,  
(1R,4S,5S)- (CA INDEX NAME)

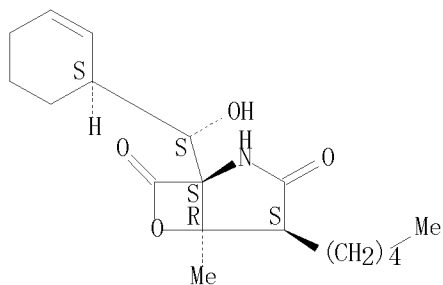
Absolute stereochemistry.



RN 1045000-73-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-pentyl-,  
(1S,4S,5R)- (CA INDEX NAME)

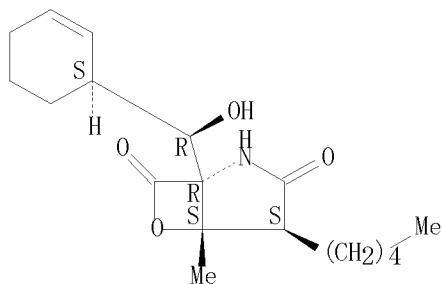
Absolute stereochemistry.



RN 1045000-74-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-pentyl-,  
(1R,4S,5S)- (CA INDEX NAME)

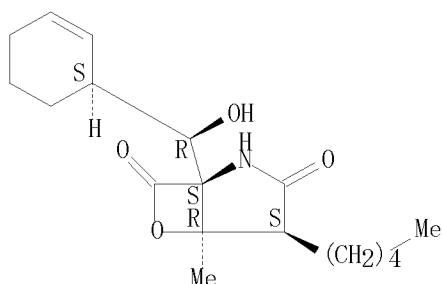
Absolute stereochemistry.



RN 1045000-75-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-pentyl-,  
(1S, 4S, 5R)- (CA INDEX NAME)

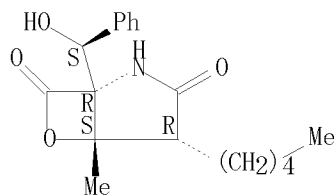
Absolute stereochemistry.



RN 1045000-84-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-5-methyl-4-pentyl-, (1R, 4R, 5S)- (CA INDEX NAME)

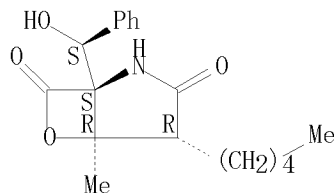
Absolute stereochemistry.



RN 1045000-85-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-5-methyl-4-pentyl-, (1S, 4R, 5R)- (CA INDEX NAME)

Absolute stereochemistry.

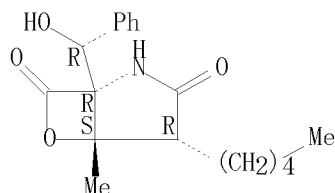


RN 1045000-86-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-5-methyl-4-pentyl-, (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.

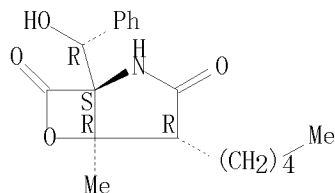




RN 1045000-87-0 CAPLUS

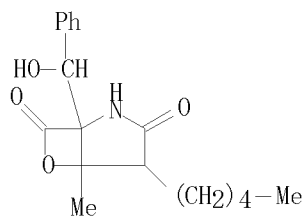
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-5-methyl-4-pentyl-, (1S,4R,5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1045000-88-1 CAPLUS

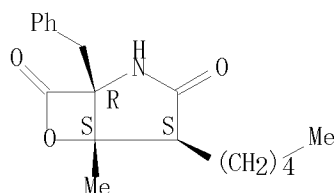
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(hydroxyphenylmethyl)-5-methyl-4-pentyl- (CA INDEX NAME)



RN 1045000-94-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
5-methyl-4-pentyl-1-(phenylmethyl)-, (1R,4S,5S)- (CA INDEX NAME)

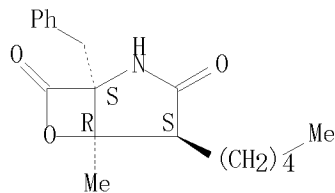
Absolute stereochemistry.



RN 1045000-95-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
5-methyl-4-pentyl-1-(phenylmethyl)-, (1S,4S,5R)- (CA INDEX NAME)

Absolute stereochemistry.

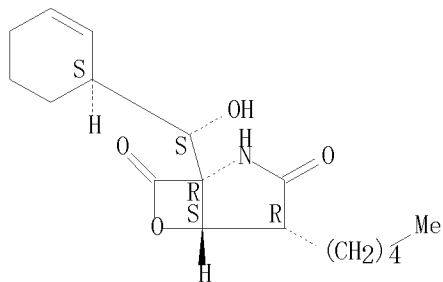


RN 1045000-96-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,

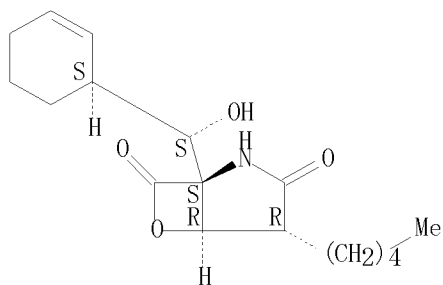
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-pentyl-, (1R, 4R, 5S)- (CA  
INDEX NAME)

Absolute stereochemistry.



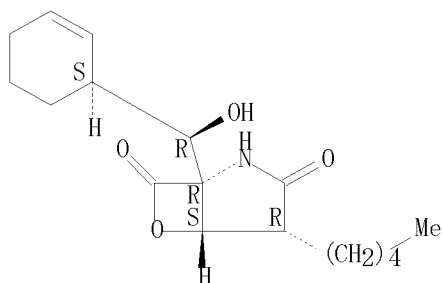
RN 1045000-97-2 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-pentyl-, (1S, 4R, 5R)- (CA  
INDEX NAME)

Absolute stereochemistry.



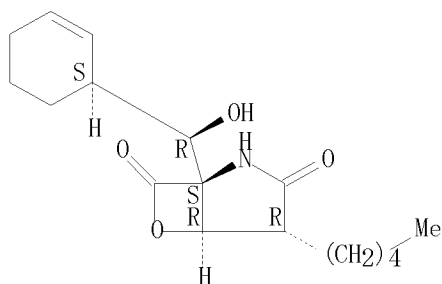
RN 1045000-98-3 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-pentyl-, (1R, 4R, 5S)- (CA  
INDEX NAME)

Absolute stereochemistry.



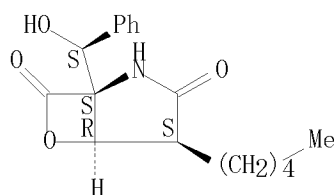
RN 1045000-99-4 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-pentyl-, (1S, 4R, 5R)- (CA  
INDEX NAME)

Absolute stereochemistry.



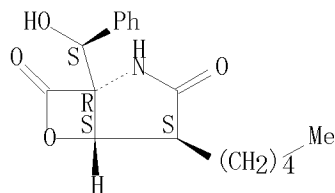
RN 1045001-08-8 CAPLUS  
 CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-hydroxyphenylmethyl]-4-pentyl-, (1S,4S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



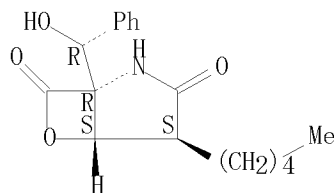
RN 1045001-09-9 CAPLUS  
 CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-hydroxyphenylmethyl]-4-pentyl-, (1R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



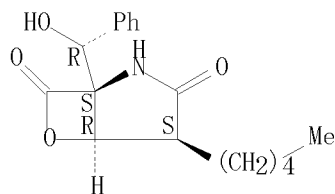
RN 1045001-10-2 CAPLUS  
 CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(R)-hydroxyphenylmethyl]-4-pentyl-, (1R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1045001-11-3 CAPLUS  
 CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(R)-hydroxyphenylmethyl]-4-pentyl-, (1S,4S,5R)- (CA INDEX NAME)

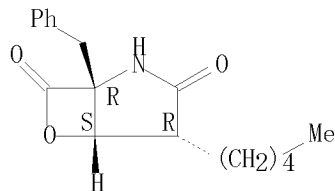
Absolute stereochemistry.



RN 1045001-17-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-pentyl-1-(phenylmethyl)-,  
(1R, 4R, 5S)- (CA INDEX NAME)

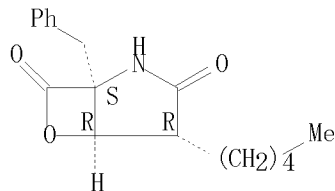
Absolute stereochemistry.



RN 1045001-18-0 CAPLUS

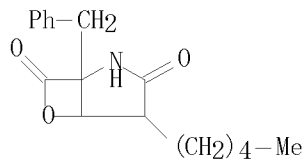
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-pentyl-1-(phenylmethyl)-,  
(1S, 4R, 5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1045001-19-1 CAPLUS

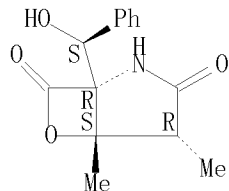
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-pentyl-1-(phenylmethyl)-  
(CA INDEX NAME)



RN 1045001-27-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-4,5-dimethyl-, (1R, 4R, 5S)- (CA INDEX NAME)

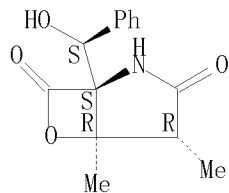
Absolute stereochemistry.



RN 1045001-28-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-4,5-dimethyl-, (1S, 4R, 5R)- (CA INDEX NAME)

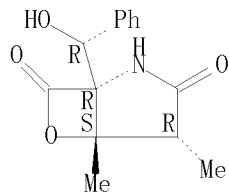
Absolute stereochemistry.



RN 1045001-29-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-4,5-dimethyl-, (1R,4R,5S)- (CA INDEX NAME)

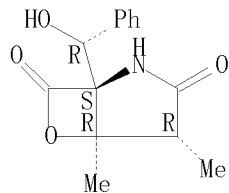
Absolute stereochemistry.



RN 1045001-30-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-4,5-dimethyl-, (1S,4R,5R)- (CA INDEX NAME)

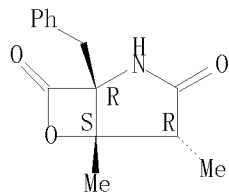
Absolute stereochemistry.



RN 1045001-36-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4,5-dimethyl-1-(phenylmethyl)-, (1R,4R,5S)- (CA INDEX NAME)

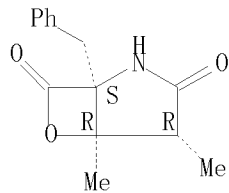
Absolute stereochemistry.



RN 1045001-37-3 CAPLUS

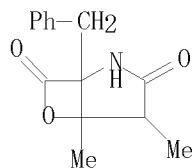
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4,5-dimethyl-1-(phenylmethyl)-, (1S,4R,5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1045001-38-4 CAPLUS

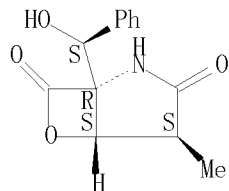
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4,5-dimethyl-1-(phenylmethyl)-  
(CA INDEX NAME)



RN 1045001-44-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-4-methyl-, (1R,4S,5S)- (CA INDEX NAME)

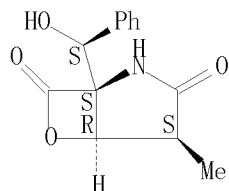
Absolute stereochemistry.



RN 1045001-45-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-4-methyl-, (1S,4S,5R)- (CA INDEX NAME)

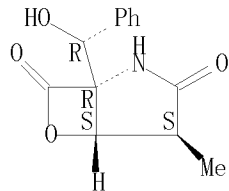
Absolute stereochemistry.



RN 1045001-46-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-4-methyl-, (1R,4S,5S)- (CA INDEX NAME)

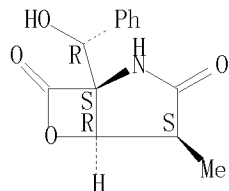
Absolute stereochemistry.



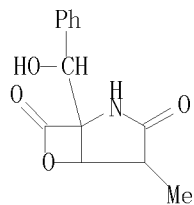
RN 1045001-47-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-4-methyl-, (1S,4S,5R)- (CA INDEX NAME)

Absolute stereochemistry.

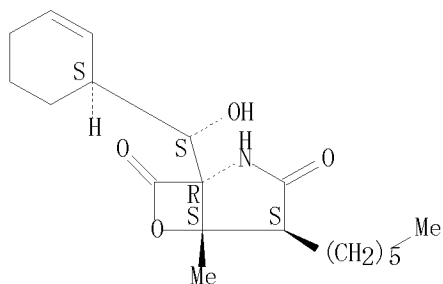


RN 1045001-48-6 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-(hydroxyphenylmethyl)-4-methyl- (CA INDEX NAME)



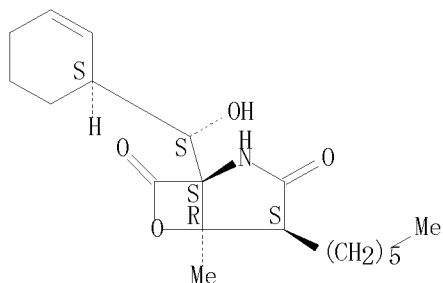
RN 1045003-06-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-, (1R,4S,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



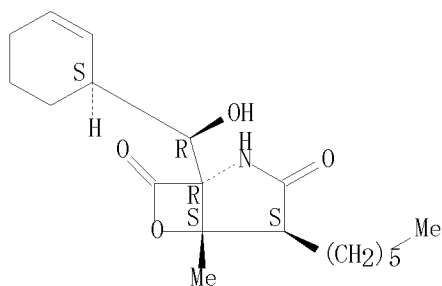
RN 1045003-07-3 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-, (1S,4S,5R)-  
 (CA INDEX NAME)

Absolute stereochemistry.



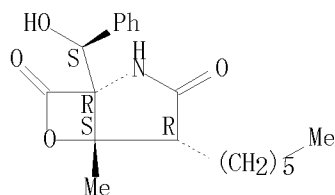
RN 1045003-08-4 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-, (1R,4S,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



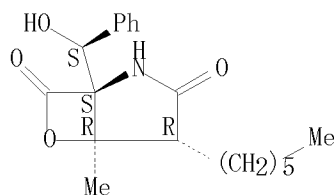
RN 1045003-16-4 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



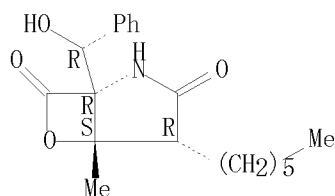
RN 1045003-17-5 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



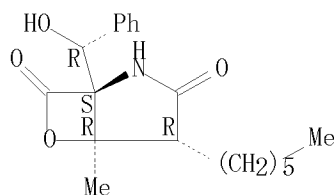
RN 1045003-18-6 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



RN 1045003-19-7 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

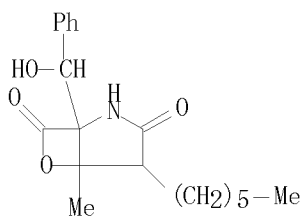
Absolute stereochemistry.



RN 1045003-20-0 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,



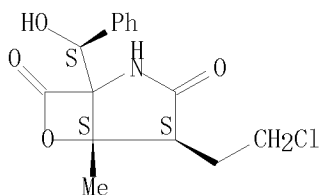
4-hexyl-1-(hydroxyphenylmethyl)-5-methyl- (CA INDEX NAME)



RN 1045003-24-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (4S,5S)- (CA  
INDEX NAME)

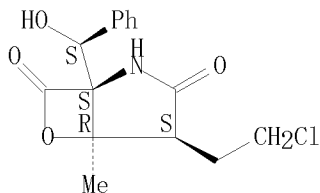
Absolute stereochemistry.



RN 1045003-25-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1S,4S,5R)- (CA  
INDEX NAME)

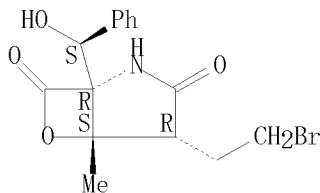
Absolute stereochemistry.



RN 1045003-29-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA  
INDEX NAME)

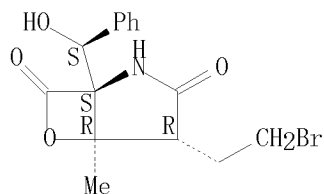
Absolute stereochemistry.



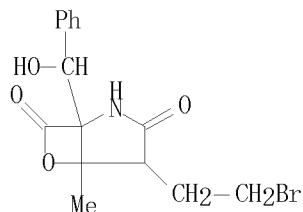
RN 1045003-31-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1S,4R,5R)- (CA  
INDEX NAME)

Absolute stereochemistry.

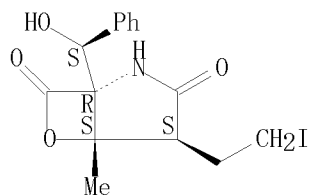


RN 1045003-32-4 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-bromoethyl)-1-(hydroxyphenylmethyl)-5-methyl- (CA INDEX NAME)



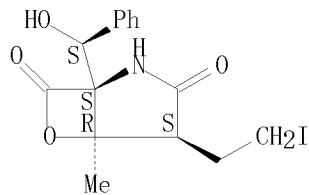
RN 1045003-37-9 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-hydroxyphenylmethyl]-4-(2-iodoethyl)-5-methyl-, (1R,4S,5S)- (CA  
 INDEX NAME)

Absolute stereochemistry.



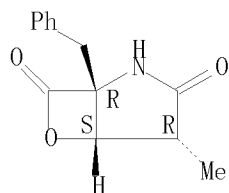
RN 1045003-38-0 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-hydroxyphenylmethyl]-4-(2-iodoethyl)-5-methyl-, (1S,4S,5R)- (CA  
 INDEX NAME)

Absolute stereochemistry.



RN 1045003-44-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-methyl-1-(phenylmethyl)-,  
 (1R,4R,5S)- (CA INDEX NAME)

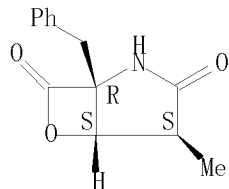
Absolute stereochemistry.



RN 1045003-45-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-methyl-1-(phenylmethyl)-,  
(1R,4S,5S)- (CA INDEX NAME)

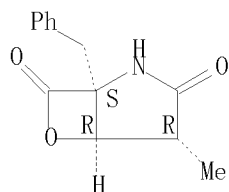
Absolute stereochemistry.



RN 1045003-46-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-methyl-1-(phenylmethyl)-,  
(1S,4R,5R)- (CA INDEX NAME)

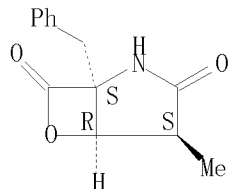
Absolute stereochemistry.



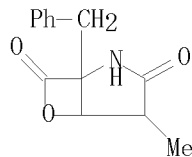
RN 1045003-47-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-methyl-1-(phenylmethyl)-,  
(1S,4S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



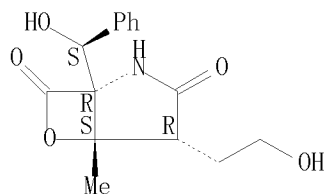
RN 1045003-48-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-methyl-1-(phenylmethyl)-  
(CA INDEX NAME)

RN 1045004-20-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-hydroxyethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA  
INDEX NAME)

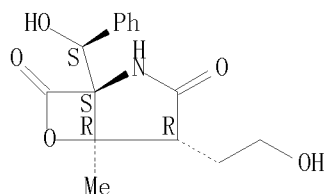
Absolute stereochemistry.



RN 1045004-21-4 CAPLUS

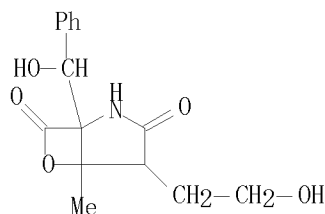
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-hydroxyethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1S,4R,5R)- (CA  
INDEX NAME)

Absolute stereochemistry.



RN 1045004-22-5 CAPLUS

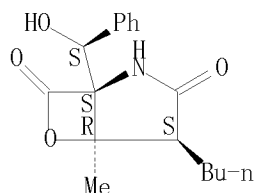
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-hydroxyethyl)-1-(hydroxyphenylmethyl)-5-methyl- (CA INDEX NAME)



RN 1045004-27-0 CAPLUS

CN INDEX NAME NOT YET ASSIGNED

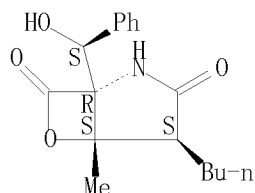
Absolute stereochemistry.



RN 1045004-28-1 CAPLUS

CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

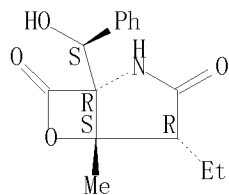


RN 1045004-33-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-ethyl-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA INDEX  
NAME)

NAME)

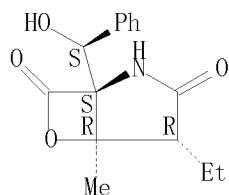
Absolute stereochemistry.



RN 1045004-34-9 CAPLUS

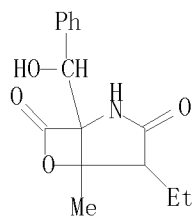
CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-ethyl-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1S, 4R, 5R)- (CA INDEX  
NAME)

Absolute stereochemistry.



RN 1045004-35-0 CAPLUS

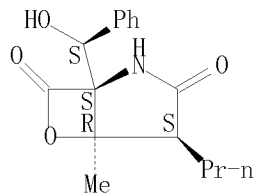
CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-ethyl-1-(hydroxyphenylmethyl)-5-methyl- (CA INDEX NAME)



RN 1045004-40-7 CAPLUS

CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-5-methyl-4-propyl-, (1S, 4S, 5R)- (CA INDEX  
NAME)

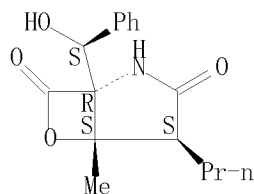
Absolute stereochemistry.



RN 1045004-41-8 CAPLUS

CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-5-methyl-4-propyl-, (1R, 4S, 5S)- (CA INDEX  
NAME)

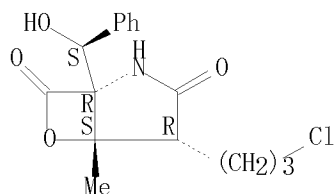
Absolute stereochemistry.



RN 1045004-45-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(3-chloropropyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA  
INDEX NAME)

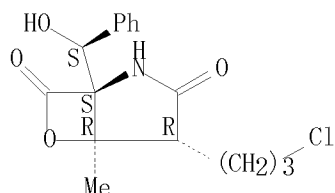
Absolute stereochemistry.



RN 1045004-47-4 CAPLUS

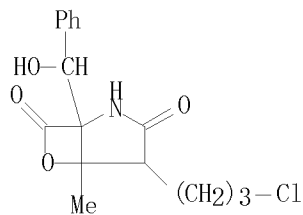
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(3-chloropropyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1S,4R,5R)- (CA  
INDEX NAME)

Absolute stereochemistry.



RN 1045004-48-5 CAPLUS

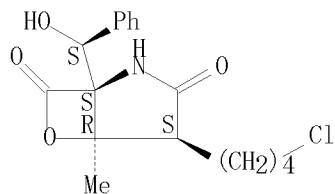
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(3-chloropropyl)-1-(hydroxyphenylmethyl)-5-methyl- (CA INDEX NAME)



RN 1045004-53-2 CAPLUS

CN INDEX NAME NOT YET ASSIGNED

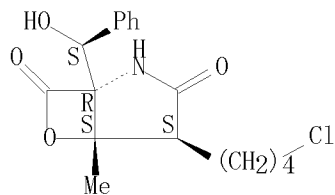
Absolute stereochemistry.



RN 1045004-54-3 CAPLUS

CN INDEX NAME NOT YET ASSIGNED

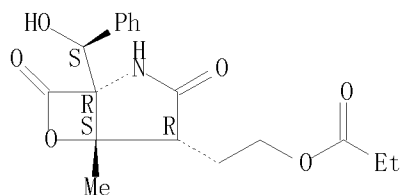
Absolute stereochemistry.



RN 1045004-59-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-,  
(1R, 4R, 5S)- (CA INDEX NAME)

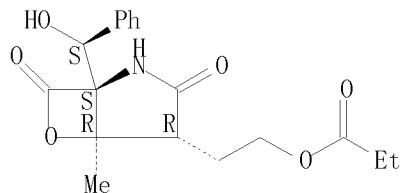
Absolute stereochemistry.



RN 1045004-60-1 CAPLUS

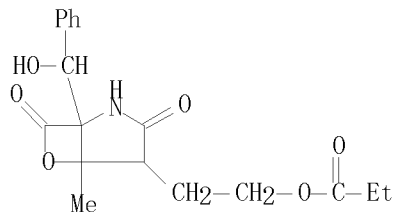
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-,  
(1S, 4R, 5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1045004-62-3 CAPLUS

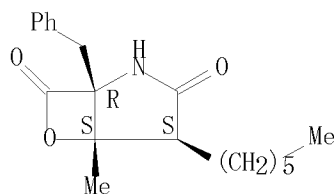
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(hydroxyphenylmethyl)-5-methyl-4-[2-(1-oxopropoxy)ethyl]- (CA INDEX NAME)



RN 1045004-67-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-hexyl-5-methyl-1-(phenylmethyl)-, (1R, 4S, 5S)- (CA INDEX NAME)

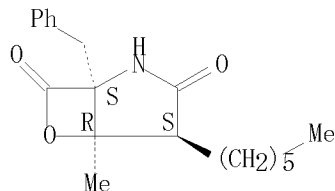
Absolute stereochemistry.



RN 1045004-68-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-hexyl-5-methyl-1-(phenylmethyl)-, (1S,4S,5R)- (CA INDEX NAME)

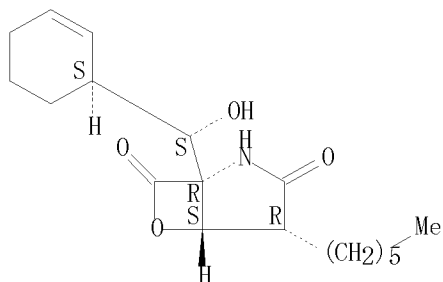
Absolute stereochemistry.



RN 1045004-69-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-, (1R,4R,5S)- (CA  
INDEX NAME)

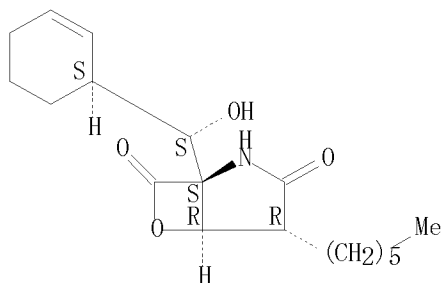
Absolute stereochemistry.



RN 1045004-70-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-, (1S,4R,5R)- (CA  
INDEX NAME)

Absolute stereochemistry.

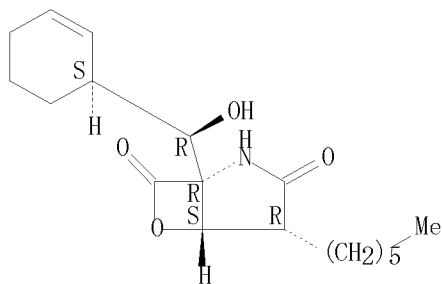


RN 1045004-71-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-, (1R,4R,5S)- (CA  
INDEX NAME)

Absolute stereochemistry.

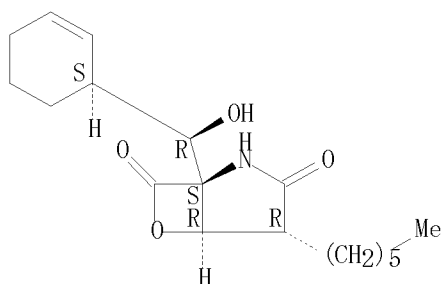




RN 1045004-72-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-, (1S, 4R, 5R)- (CA  
INDEX NAME)

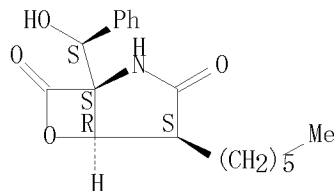
Absolute stereochemistry.



RN 1045004-81-6 CAPLUS

CN INDEX NAME NOT YET ASSIGNED

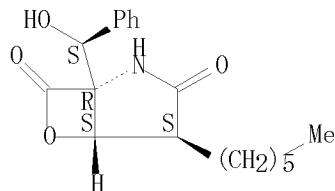
Absolute stereochemistry.



RN 1045004-82-7 CAPLUS

CN INDEX NAME NOT YET ASSIGNED

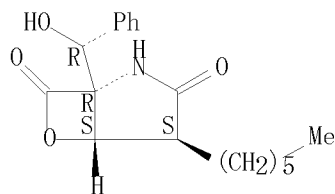
Absolute stereochemistry.



RN 1045004-83-8 CAPLUS

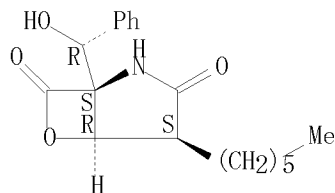
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



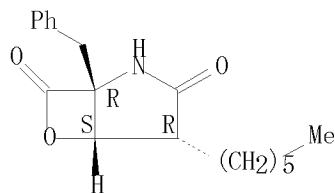
RN 1045004-84-9 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



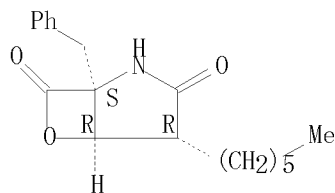
RN 1045004-90-7 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-hexyl-1-(phenylmethyl)-,  
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.

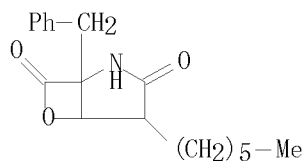


RN 1045004-91-8 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-hexyl-1-(phenylmethyl)-,  
(1S, 4R, 5R)- (CA INDEX NAME)

Absolute stereochemistry.

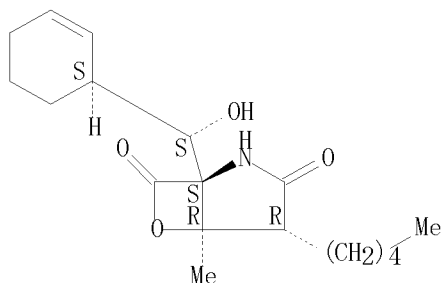


RN 1045004-92-9 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-hexyl-1-(phenylmethyl)- (CA  
INDEX NAME)



RN 1045004-93-0 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-pentyl-,  
(1S, 4R, 5R)- (CA INDEX NAME)

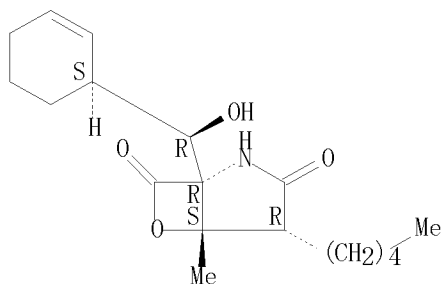
Absolute stereochemistry.



RN 1045008-27-2 CAPLUS

CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-pentyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

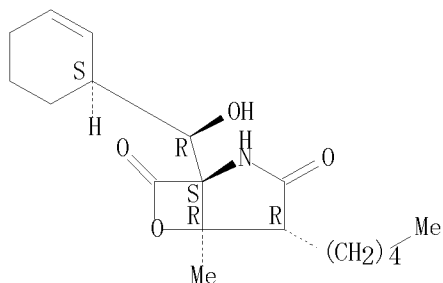
Absolute stereochemistry.



RN 1045008-28-3 CAPLUS

CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-pentyl-,  
(1S, 4R, 5R)- (CA INDEX NAME)

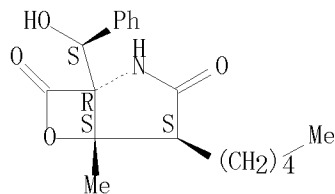
Absolute stereochemistry.



RN 1045008-37-4 CAPLUS

CN 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-5-methyl-4-pentyl-, (1R, 4S, 5S)- (CA INDEX NAME)

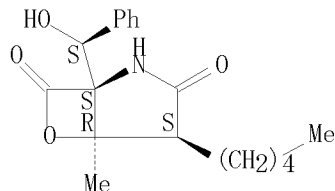
Absolute stereochemistry.



RN 1045008-38-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-5-methyl-4-pentyl-, (1S,4S,5R)- (CA INDEX  
NAME)

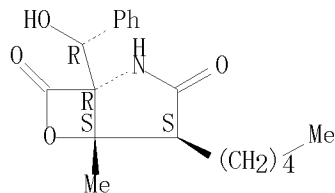
Absolute stereochemistry.



RN 1045008-39-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-5-methyl-4-pentyl-, (1R,4S,5S)- (CA INDEX  
NAME)

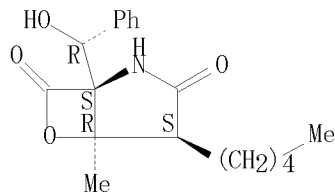
Absolute stereochemistry.



RN 1045008-40-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-5-methyl-4-pentyl-, (1S,4S,5R)- (CA INDEX  
NAME)

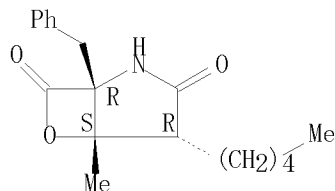
Absolute stereochemistry.



RN 1045008-46-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
5-methyl-4-pentyl-1-(phenylmethyl)-, (1R,4R,5S)- (CA INDEX NAME)

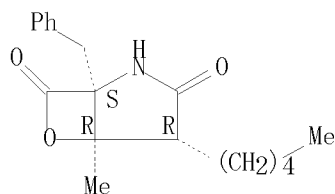
Absolute stereochemistry.



RN 1045008-47-6 CAPLUS

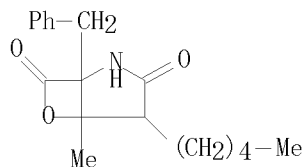
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
5-methyl-4-pentyl-1-(phenylmethyl)-, (1S,4R,5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1045008-48-7 CAPLUS

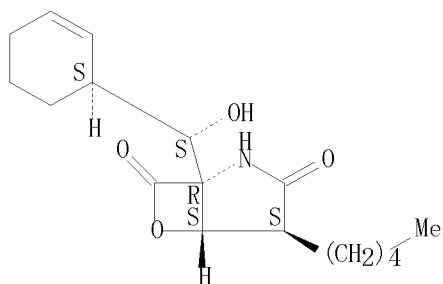
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
5-methyl-4-pentyl-1-(phenylmethyl)- (CA INDEX NAME)



RN 1045008-49-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-pentyl-, (1R,4S,5S)- (CA  
INDEX NAME)

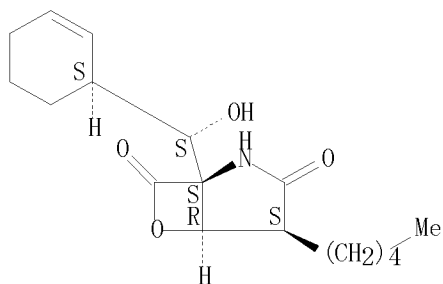
Absolute stereochemistry.



RN 1045008-50-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-pentyl-, (1S,4S,5R)- (CA  
INDEX NAME)

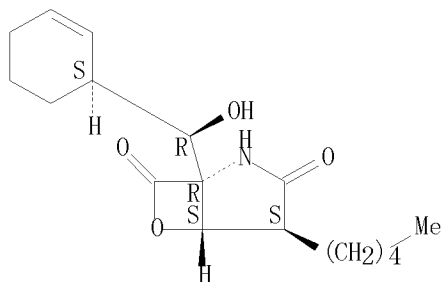
Absolute stereochemistry.



RN 1045008-51-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-pentyl-, (1R,4S,5S)- (CA  
INDEX NAME)

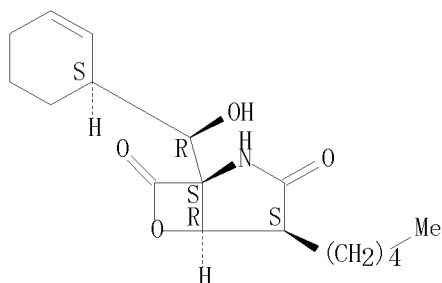
Absolute stereochemistry.



RN 1045008-52-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-pentyl-, (1S,4S,5R)- (CA  
INDEX NAME)

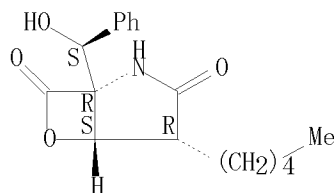
Absolute stereochemistry.



RN 1045008-61-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-4-pentyl-, (1R,4R,5S)- (CA INDEX NAME)

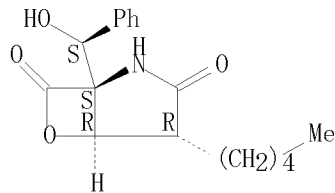
Absolute stereochemistry.



RN 1045008-62-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-4-pentyl-, (1S,4R,5R)- (CA INDEX NAME)

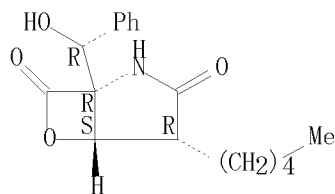
Absolute stereochemistry.



RN 1045008-63-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-4-pentyl-, (1R,4R,5S)- (CA INDEX NAME)

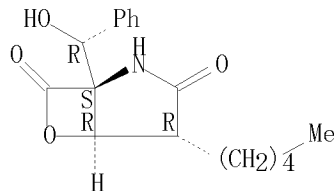
Absolute stereochemistry.



RN 1045008-64-7 CAPLUS

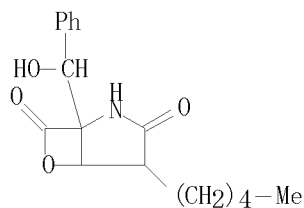
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-4-pentyl-, (1S,4R,5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1045008-65-8 CAPLUS

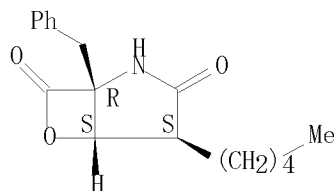
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(hydroxyphenylmethyl)-4-pentyl- (CA INDEX NAME)



RN 1045008-71-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-pentyl-1-(phenylmethyl)-,  
(1R,4S,5S)- (CA INDEX NAME)

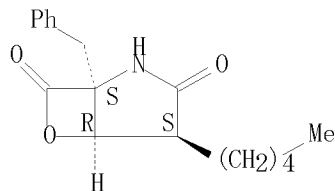
Absolute stereochemistry.



RN 1045008-72-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-pentyl-1-(phenylmethyl)-,  
(1S,4S,5R)- (CA INDEX NAME)

Absolute stereochemistry.

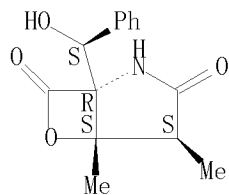


RN 1045008-80-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,

1-[(S)-hydroxyphenylmethyl]-4,5-dimethyl-, (1R,4S,5S)- (CA INDEX NAME)

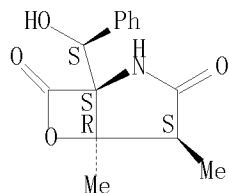
Absolute stereochemistry.



RN 1045008-81-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-4,5-dimethyl-, (1S,4S,5R)- (CA INDEX NAME)

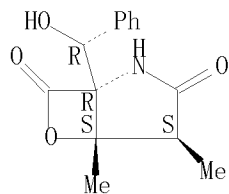
Absolute stereochemistry.



RN 1045008-82-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-4,5-dimethyl-, (1R,4S,5S)- (CA INDEX NAME)

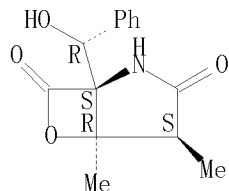
Absolute stereochemistry.



RN 1045008-83-0 CAPLUS

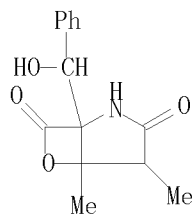
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-4,5-dimethyl-, (1S,4S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1045008-84-1 CAPLUS

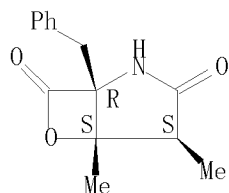
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(hydroxyphenylmethyl)-4,5-dimethyl- (CA INDEX NAME)





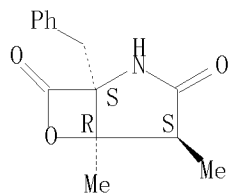
RN 1045008-90-9 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4,5-dimethyl-1-(phenylmethyl)-, (1R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



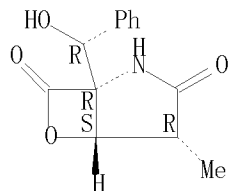
RN 1045008-91-0 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4,5-dimethyl-1-(phenylmethyl)-, (1S,4S,5R)- (CA INDEX NAME)

Absolute stereochemistry.



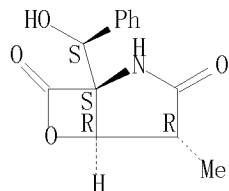
RN 1045008-99-8 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-4-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



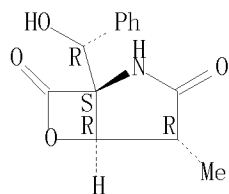
RN 1045009-00-4 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-4-methyl-, (1S,4R,5R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 1045009-01-5 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-hydroxyphenylmethyl]-4-methyl-, (1S,4R,5R)- (CA INDEX NAME)

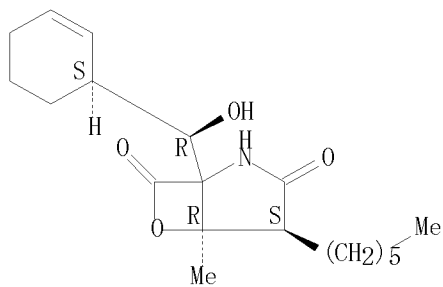
Absolute stereochemistry.



RN 1071908-05-8 CAPLUS

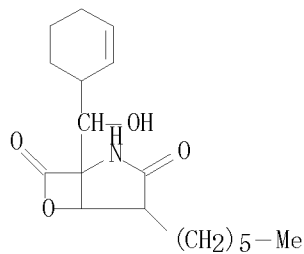
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-, (4S,5R)-  
(CA INDEX NAME)

Absolute stereochemistry.



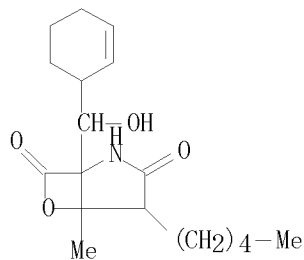
RN 1071955-02-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(2-cyclohexen-1-ylhydroxymethyl)-4-hexyl- (CA INDEX NAME)



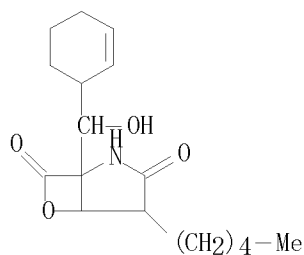
RN 1071955-11-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(2-cyclohexen-1-ylhydroxymethyl)-5-methyl-4-pentyl- (CA INDEX NAME)

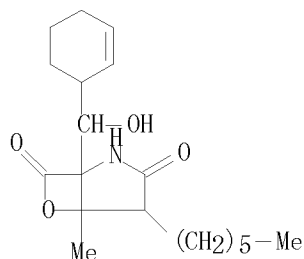


RN 1071955-28-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(2-cyclohexen-1-ylhydroxymethyl)-4-pentyl- (CA INDEX NAME)

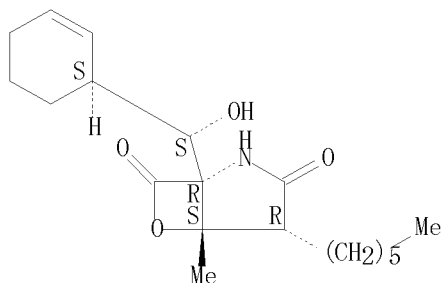


RN 1089667-54-8 CAPLUS  
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 1-(2-cyclohexen-1-ylhydroxymethyl)-4-hexyl-5-methyl- (CA INDEX NAME)



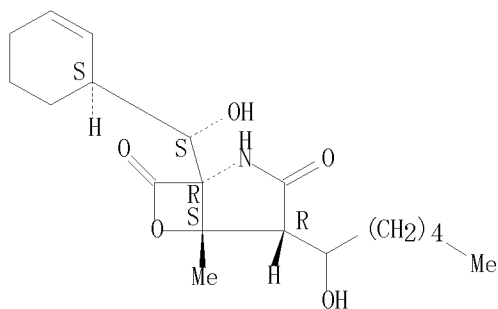
IT 744200-66-6P 744200-67-7P 744200-68-8P  
 RL: AGR (Agricultural use); BPN (Biosynthetic preparation); BIOL  
 (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of substituted 2-pyrrolidone derivs. as agrochem. fungicides  
 and insecticides)  
 RN 744200-66-6 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 744200-67-7 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(1-hydroxyhexyl)-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

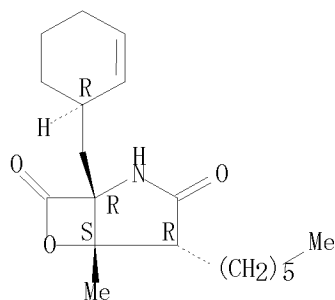
Absolute stereochemistry.



RN 744200-68-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(1R)-2-cyclohexen-1-ylmethyl]-4-hexyl-5-methyl-, (1R, 4R, 5S)- (CA INDEX  
NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	2	THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT:	8	THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

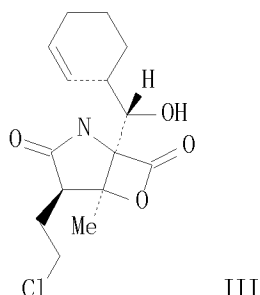
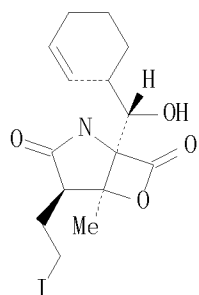
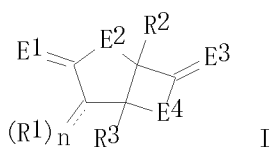
L6 ANSWER 154 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2005:1348855 CAPLUS  
 DOCUMENT NUMBER: 144:81222  
 TITLE: Preparation of [3.2.0] heterocyclic compounds and  
 treatment methods of using the same  
 INVENTOR(S): Potts, Barbara Christine; Macherla, Venkat; Mitchell,  
 Scott Sherman; Manam, Ram Rao; Reed, Katherine; Lam,  
 Kin Sing; Neuteboom, Saskia; Chao, Ta-Hsiang;  
 Nicholson, Benjamin; Billstrom, Cheryl  
 PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
 SOURCE: U.S. Pat. Appl. Publ., 94 pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 5  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050288352	A1	20051229	US 2005-118260	20050429
US 7276530	B2	20071002		
AU 2005283141	A1	20060316	AU 2005-283141	20050429
CA 2565235	A1	20060316	CA 2005-2565235	20050429
WO 2006028525	A2	20060316	WO 2005-US14846	20050429
WO 2006028525	A3	20070518		
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BR 2005009824	A	20071009	BR 2005-9824	20050429
CN 101061120	A	20071024	CN 2005-80019345	20050429
JP 2007535559	T	20071206	JP 2007-511021	20050429
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EP 2266988	A1	20101229	EP 2010-179249	20050429
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US 20060264495	A1	20061123	US 2006-412476	20060427
US 20070004676	A1	20070104	US 2006-453374	20060615
US 7579371	B2	20090825		
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ZA 2006009778	A	20091028	ZA 2006-9778	20061123
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US 7544814	B2	20090609		
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			US 2005-644132P	P 20050113
			US 2005-659385P	P 20050304
			EP 2005-818192	A3 20050429
			EP 2008-168314	A3 20050429
			US 2005-118260	A2 20050429
			US 2005-676533P	P 20050429
			WO 2005-US14846	W 20050429
			US 2006-412476	A2 20060427

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S):  
GRAPHIC IMAGE:

MARPAT 144:81222



#### ABSTRACT:

[3.2.0]-Bicycloheptanes I [R1 = H, halo, (un)substituted alkyl, etc.; R2 = H, halo, (un)substituted alkyl, alkenyl, etc.; R3 = halo, (un)substituted aryl, cycloalkyl, etc.; E1-4 independently = (un)substituted heteroatom; with provisions] and derivs. thereof, are prepared and disclosed as having anti-cancer, anti-inflammatory, and anti-microbial properties. Thus, e.g., II was prepared by iodination of fermentation product III. In assays of growth inhibition of human multiple myeloma, II for example demonstrated EC50 values (nM) of 5.9 and 3.2 resp. against RPMI 8226 and U266 cell lines. Pharmaceutical compns. comprising such compds. and methods of treating cancer, inflammatory conditions, and microbial infections with the disclosed compds. or the disclosed pharmaceutical compns. are also disclosed.

IT 1044999-00-9      1057246-19-1      1057246-20-4  
1057246-22-6      1057246-23-7      1057246-24-8  
1057246-25-9      1067236-86-5      1067237-13-1

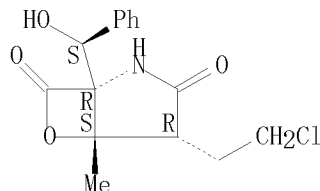
RL: PRPH (Prophetic)

(Preparation of [3.2.0] heterocyclic compounds and treatment methods of using the same)

RN 1044999-00-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

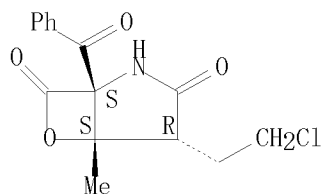
Absolute stereochemistry.



RN 1057246-19-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-benzoyl-4-(2-chloroethyl)-5-methyl-, (1S,4R,5S)- (CA INDEX NAME)

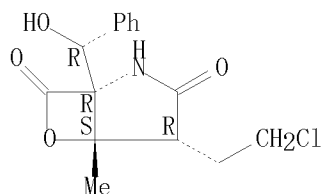
Absolute stereochemistry.



RN 1057246-20-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-hydroxyphenylmethyl]-5-methyl-, (1R,4R,5S)- (CA  
INDEX NAME)

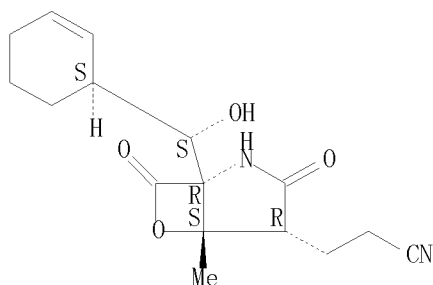
Absolute stereochemistry.



RN 1057246-22-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-4-propanenitrile,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-,  
(1R,4R,5S)- (CA INDEX NAME)

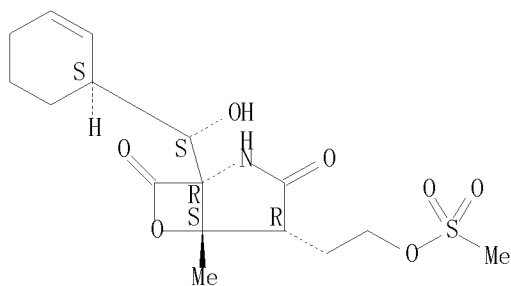
Absolute stereochemistry.



RN 1057246-23-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-  
[(methylsulfonyl)oxy]ethyl]-, (1R,4R,5S)- (CA INDEX NAME)

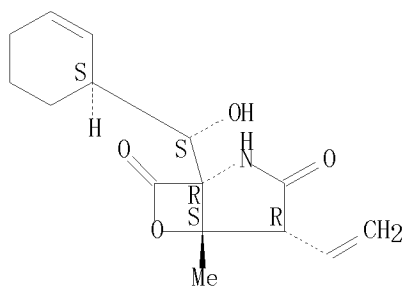
Absolute stereochemistry.



RN 1057246-24-8 CAPLUS

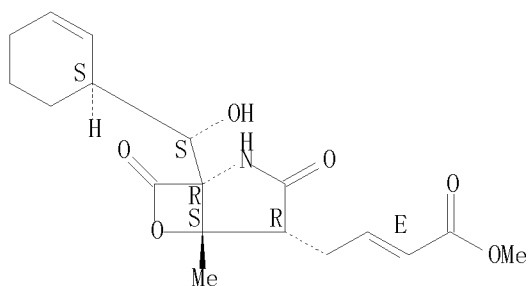
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethenyl-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



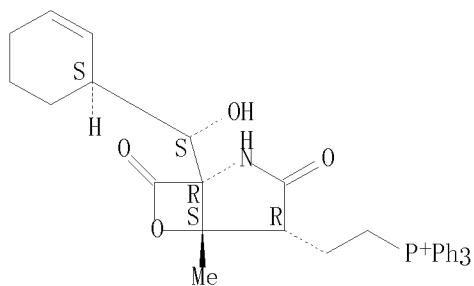
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CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.  
Double bond geometry as shown.



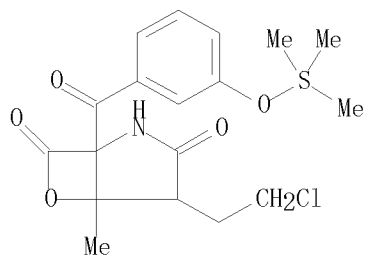
RN 1067236-86-5 CAPLUS  
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



● I<sup>-</sup>

RN 1067237-13-1 CAPLUS  
CN Sulfur, [(1S, 4R, 5S)-4-(2-chloroethyl)-1-[3-(hydroxy-κO) benzoyl]-5-methyl-6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dionato] trimethyl-, (T-4)- (CA INDEX NAME)





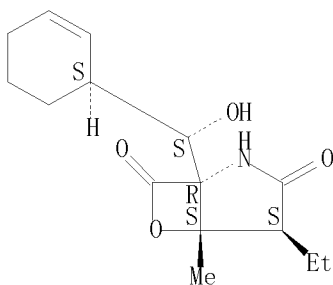
IT **872360-16-2P**

RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (preparation and MSBAR of oxazabicycloheptanes obtained via fermentation process for treatment of cancer, inflammatory conditions, and microbial infections)

RN 872360-16-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4S,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.

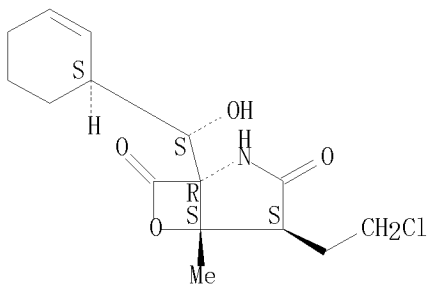
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RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation and MSBAR of oxazabicycloheptanes obtained via fermentation process for treatment of cancer, inflammatory conditions, and microbial infections)

RN 872360-11-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

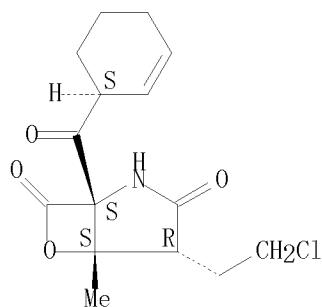
IT **872360-17-3P** **872360-18-4P**

RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (preparation and MSBAR of oxazabicycloheptanes obtained via fermentation process for treatment of cancer, inflammatory conditions, and microbial infections)

RN 872360-17-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(1S)-2-cyclohexen-1-ylcarbonyl]-5-methyl-,  
 (1S,4R,5S)- (CA INDEX NAME)

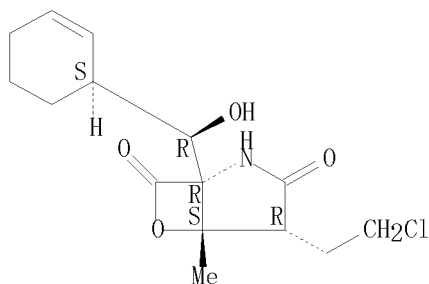
Absolute stereochemistry.



RN 872360-18-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(R)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



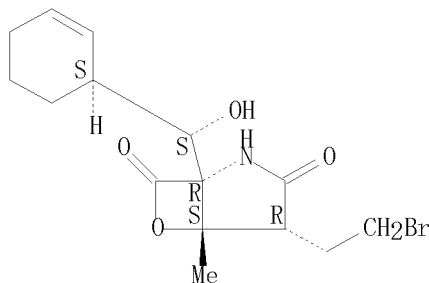
IT **872360-15-1P**

RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation and MSBAR of oxaazabicycloheptanes obtained via fermentation process for treatment of cancer, inflammatory conditions, and microbial infections)

RN 872360-15-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 823229-34-1P      823229-54-5P      823229-56-7P  
872360-22-0P      872360-23-1P      872360-24-2P

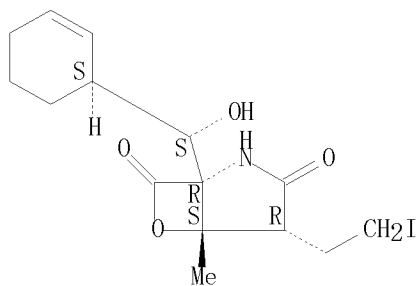
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation and MSBAR of oxaazabicycloheptanes obtained via fermentation process for treatment of cancer, inflammatory conditions, and microbial infections)

RN 823229-34-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,

1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

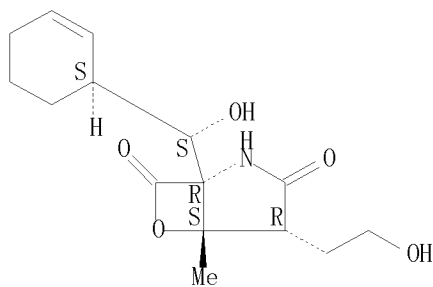
Absolute stereochemistry.



RN 823229-54-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
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(1R, 4R, 5S)- (CA INDEX NAME)

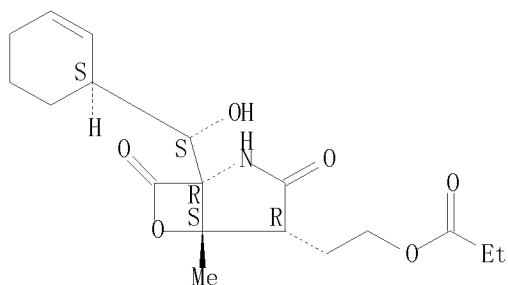
Absolute stereochemistry. Rotation (-).



RN 823229-56-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-, (1R, 4R, 5S)- (CA INDEX NAME)

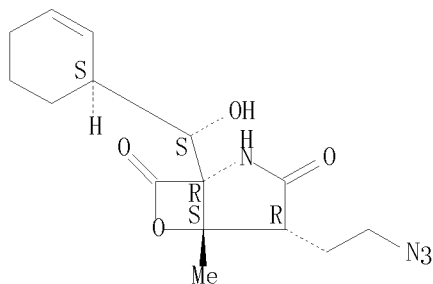
Absolute stereochemistry.



RN 872360-22-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-azidoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R, 4R, 5S)- (CA INDEX NAME)

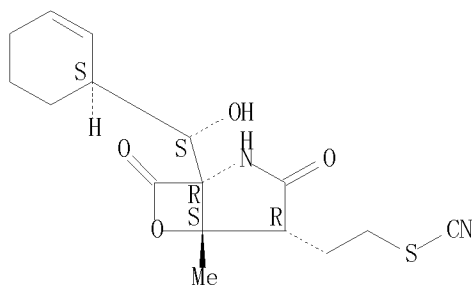
Absolute stereochemistry.



RN 872360-23-1 CAPLUS

CN Thiocyanic acid, 2-[(1R, 4R, 5S)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-3,7-dioxo-6-oxa-2-azabicyclo[3.2.0]hept-4-yl]ethyl ester (CA INDEX NAME)

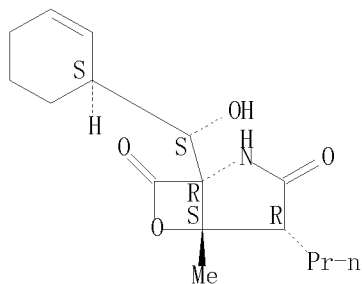
Absolute stereochemistry.



RN 872360-24-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-propyl-, (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 823229-26-1P 872360-12-8P 872360-13-9P  
872360-14-0P

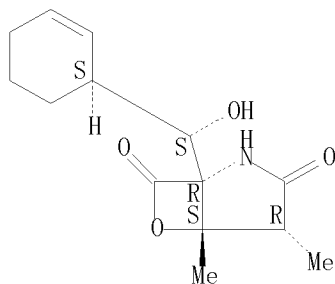
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation and MSBAR of oxazabicycloheptanes obtained via fermentation process for treatment of cancer, inflammatory conditions, and microbial infections)

RN 823229-26-1 CAPLUS

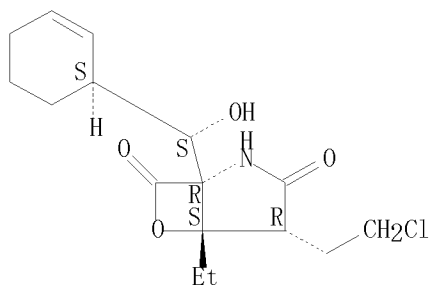
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



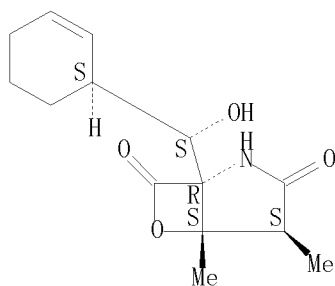
RN 872360-12-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-ethyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

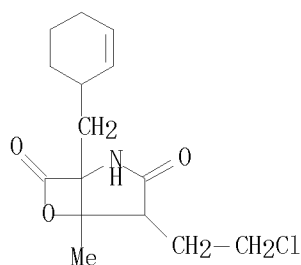


RN 872360-13-9 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4S,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



RN 872360-14-0 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-(2-cyclohexen-1-ylmethyl)-5-methyl- (CA INDEX NAME)



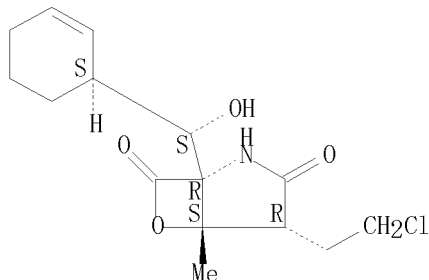
IT 437742-34-2P 863126-95-8P

RL: BPN (Biosynthetic preparation); RCT (Reactant); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
(preparation and MSBAR of oxaazabicycloheptanes obtained via fermentation process for treatment of cancer, inflammatory conditions, and microbial infections)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

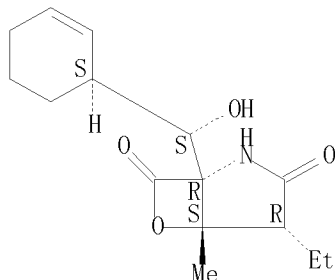
Absolute stereochemistry. Rotation (-).



RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD  
(8 CITINGS)

REFERENCE COUNT: 257 THERE ARE 257 CITED REFERENCES AVAILABLE FOR  
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L6 ANSWER 155 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2005:1293359 CAPLUS

DOCUMENT NUMBER: 144:142310

TITLE: A novel orally active proteasome inhibitor induces apoptosis in multiple myeloma cells with mechanisms distinct from bortezomib

AUTHOR(S): Chauhan, Dharminder; Catley, Laurence; Li, Guilan; Podar, Klaus; Hideshima, Teru; Velankar, Mugdha; Mitsiades, Constantine; Mitsiades, Nicolas; Yasui, Hiroshi; Letai, Anthony; Ovaa, Huib; Berkers, Celia; Nicholson, Benjamin; Chao, Ta-Hsiang; Neuteboom, Saskia T. C.; Richardson, Paul; Palladino, Michael A.; Anderson, Kenneth C.

CORPORATE SOURCE: The Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115, USA

SOURCE: Cancer Cell (2005), 8(5), 407-419

CODEN: CCAECI; ISSN: 1535-6108

PUBLISHER: Cell Press

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

Bortezomib therapy has proven successful for the treatment of relapsed and/or refractory multiple myeloma (MM); however, prolonged treatment is associated with toxicity and development of drug resistance. Here, the authors show that the novel proteasome inhibitor NPI-0052 induces apoptosis in MM cells resistant to conventional and bortezomib therapies. NPI-0052 is distinct from bortezomib in its chemical structure, effects on proteasome activities, mechanisms of action, and toxicity profile against normal cells. Moreover, NPI-0052 is orally bioactive. In animal tumor model studies, NPI-0052 is well tolerated and prolongs survival, with significantly reduced tumor recurrence. Combining NPI-0052 and bortezomib induces synergistic anti-MM activity. Our study therefore provides the rationale for clin. protocols evaluating NPI-0052, alone and together with bortezomib, to improve patient outcome in MM.

IT 437742-34-2, NPI 0052

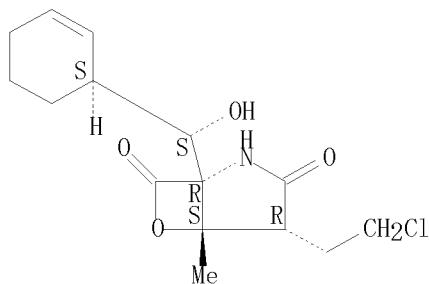
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(novel orally active proteasome inhibitor, NPI-0052, induces apoptosis in multiple myeloma cells with mechanisms distinct from bortezomib)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

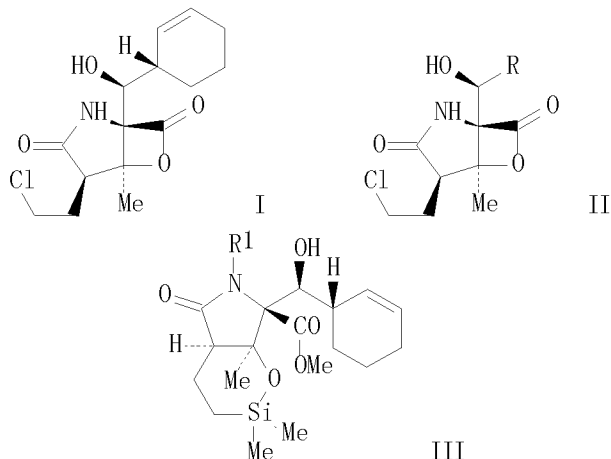


OS.CITING REF COUNT: 239 THERE ARE 239 CAPLUS RECORDS THAT CITE THIS RECORD (239 CITINGS)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 156 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2005:1154365 CAPLUS  
 DOCUMENT NUMBER: 143:422201  
 TITLE: Preparation of salinosporamide A for use in anticancer pharmaceutical compositions as proteasome inhibitors  
 INVENTOR(S): Corey, Elias J.  
 PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA  
 SOURCE: PCT Int. Appl., 66 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005099687	A2	20051027	WO 2005-US12113	20050411
WO 2005099687	A3	20051229		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20070161693	A1	20070712	US 2006-539648	20061009
US 7511156	B2	20090331		
PRIORITY APPLN. INFO.:			US 2004-560877P	P 20040409
			WO 2005-US12113	A1 20050411
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT				
OTHER SOURCE(S):		CASREACT 143:422201; MARPAT 143:422201		
GRAPHIC IMAGE:				



# ABSTRACT:

Salinosporamide A (I) and its analogs, such as II (R = alkyl, alkenyl, etc.), were enantioselectively synthesized starting from N-(4-methoxybenzoyl)-L-threonine Me ester via several novel synthetic intermediates, such as lactam II (R1 = CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-4-OMe). The compds. of this invention have been shown to inhibit the proteasome, an intracellular enzyme complex that destroys proteins the cell no longer needs. Without the proteasome, proteins would build up and clog cellular machinery. Fast-growing cancer cells make especially heavy use of the proteasome, so thwarting its action is a compelling drug strategy.

IT 437742-34-2P, (-)-Salinosporamide A  
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological



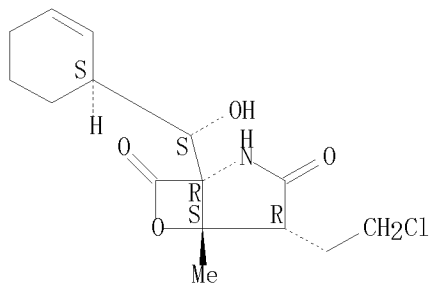
study); PREP (Preparation); USES (Uses)

(preparation of salinosporamide A for use in anticancer pharmaceutical compns. as proteasome inhibitors)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

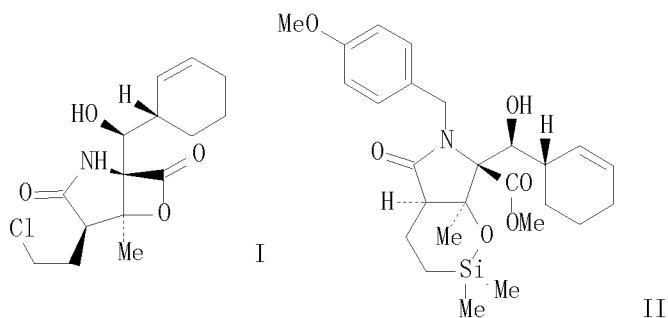
Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	4	THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT:	4	THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 157 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2005:1106831 CAPLUS  
 DOCUMENT NUMBER: 143:386848  
 TITLE: Simple stereocontrolled synthesis of salinosporamide A  
 INVENTOR(S): Corey, Elias J.  
 PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA  
 SOURCE: U.S. Pat. Appl. Publ., 17 pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050228186	A1	20051013	US 2004-821621	20040409
US 7183417	B2	20070227		
AU 2005245780	A1	20051201	AU 2005-245780	20050411
CA 2570482	A1	20051201	CA 2005-2570482	20050411
CA 2570482	C	20100810		
WO 2005113558	A2	20051201	WO 2005-US12218	20050411
WO 2005113558	A3	20051222		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1745048	A2	20070124	EP 2005-778185	20050411
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
PRIORITY APPLN. INFO.:		US 2004-821621 A 20040409		
		WO 2005-US12218 W 20050411		
OTHER SOURCE(S):		CASREACT 143:386848		
GRAPHIC IMAGE:				



# ABSTRACT:

A simple and effective stereocontrolled synthesis of (-)-salinosporamide A (I) was disclosed. The process, the first total synthesis of salinosporamide A, is capable of providing the compound in substantial quantities for further biol. studies. The disclosed synthetic scheme started from N-(4-methoxybenzoyl)-L-threonine Me ester and included the preparation of several novel synthetic intermediate compds., such as lactam II. Salinosporamide A is a synthetic target of special interest because it has previously shown proteasome inhibiting activity and shown cytotoxic activity in vitro against many tumor cell lines (IC50 values of 10 nM or less).

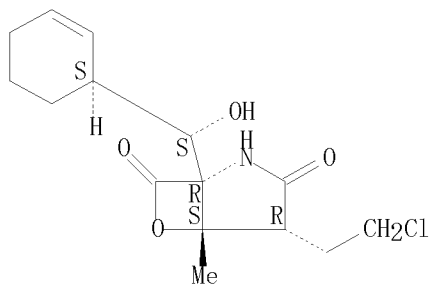
IT **437742-34-2P**

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (asym. synthesis of salinosporamide A)

RN 437742-34-2 CAPLUS

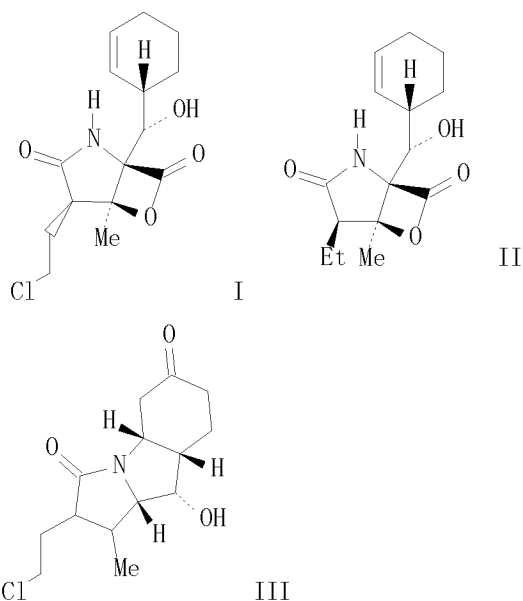
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD  
(4 CITINGS)  
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 158 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2005:567385 CAPLUS  
 DOCUMENT NUMBER: 143:244731  
 TITLE: New cytotoxic salinosporamides from the marine  
 actinomycete *Salinispora tropica*  
 AUTHOR(S): Williams, Philip G.; Buchanan, Greg O.; Feling, Robert  
 H.; Kauffman, Christopher A.; Jensen, Paul R.;  
 Fenical, William  
 CORPORATE SOURCE: Center for Marine Biotechnology and Biomedicine,  
 Scripps Institution of Oceanography, University of  
 California-San Diego, La Jolla, CA, 92093-0204, USA  
 SOURCE: Journal of Organic Chemistry (2005), 70(16), 6196-6203  
 CODEN: JOCEAH; ISSN: 0022-3263  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GRAPHIC IMAGE:



# ABSTRACT:

An extensive study of the secondary metabolites produced by the obligate marine actinomycete *S. tropica* (strain CNB-392), the producing microbe of the potent proteasome inhibitor salinosporamide A (I), has led to the isolation of 7 related  $\gamma$ -lactams. The most important of these compds. were salinosporamide B (II), which is the deschloro analog of I, and salinosporamide C (III), which is a decarboxylated pyrrole analog. New SAR data for all 8 compds., derived from extensive testing against the human colon carcinoma HCT-116 and the 60-cell-line panel at the NCI, indicate that the chloroethyl moiety plays a major role in the enhanced activity of I.

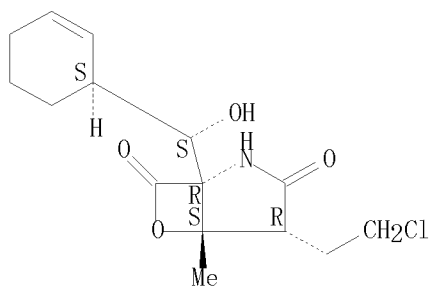
IT **437742-34-2**, Salinosporamide A

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (new cytotoxic salinosporamides from the marine actinomycete  
*Salinispora tropica*)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



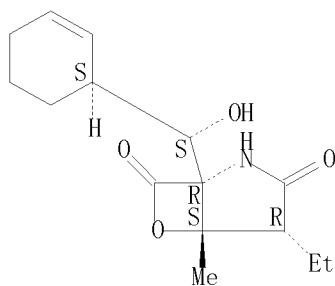
IT **863126-95-8P**, Salinosporamide B

RL: BSU (Biological study, unclassified); NPO (Natural product occurrence); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)  
(new cytotoxic salinosporamides from the marine actinomycete *Salinispora tropica*)

RN 863126-95-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

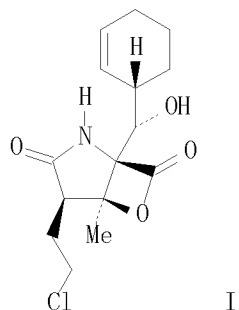
Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 83 THERE ARE 83 CAPLUS RECORDS THAT CITE THIS RECORD (84 CITINGS)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 159 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2005:421879 CAPLUS  
 DOCUMENT NUMBER: 143:153185  
 TITLE: Total Synthesis of Salinosporamide A  
 AUTHOR(S): Endo, Atsushi; Danishefsky, Samuel J.  
 CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, Sloan-Kettering  
 Institute for Cancer Research, New York, NY, 10021,  
 USA  
 SOURCE: Journal of the American Chemical Society (2005),  
 127(23), 8298-8299  
 CODEN: JACSAT; ISSN: 0002-7863  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 143:153185  
 GRAPHIC IMAGE:



## ABSTRACT:

Total synthesis of potent proteasome inhibitor salinosporamide A (I) has been accomplished, which features strictly substrate-controlled operations starting with the only chiral center of (R)-pyroglutamic acid. The consecutive quaternary carbons within I have been efficiently constructed by manipulation of two intramol. reactions: carbonate-mediated internal acylation of an imide ester and selenocyclization of aldehyde to exocyclic methylene group.

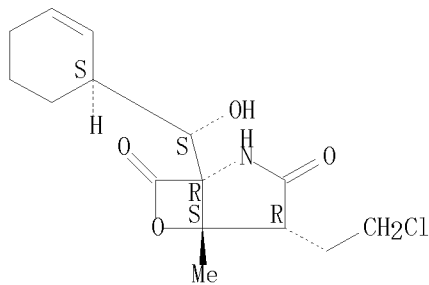
IT 437742-34-2P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (total synthesis of salinosporamide A)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 62 THERE ARE 62 CAPLUS RECORDS THAT CITE THIS  
 RECORD (62 CITINGS)  
 REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 160 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2005:383219 CAPLUS  
 DOCUMENT NUMBER: 143:70990  
 TITLE: Structure-Activity Relationship Studies of  
 Salinosporamide A (NPI-0052), a Novel Marine Derived  
 Proteasome Inhibitor  
 AUTHOR(S): Macherla, Venkat R.; Mitchell, Scott S.; Manam, Rama  
 Rao; Reed, Katherine A.; Chao, Ta-Hsiang; Nicholson,  
 Benjamin; Deyanat-Yazdi, Gordafaried; Mai, Bao;  
 Jensen, Paul R.; Fenical, William F.; Neuteboom,  
 Saskia T. C.; Lam, Kin S.; Palladino, Michael A.;  
 Potts, Barbara C. M.  
 CORPORATE SOURCE: Nereus Pharmaceuticals, Inc., San Diego, CA, 92121,  
 USA  
 SOURCE: Journal of Medicinal Chemistry (2005), 48(11),  
 3684-3687  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 143:70990

ABSTRACT:  
 Salinosporamide A (1, NPI-0052) is a potent proteasome inhibitor in development  
 for treating cancer. In this study, a series of analogs was assayed for  
 cytotoxicity, proteasome inhibition, and inhibition of NF- $\kappa$ B activation.  
 Marked redns. in potency in cell-based assays accompanied replacement of the  
 chloroethyl group with unhalogenated substituents. Halogen exchange and  
 cyclohexene ring epoxidn. were well tolerated, while some stereochem.  
 modifications significantly attenuated activity. These findings provide  
 insights into structure-activity relationships within this novel series.

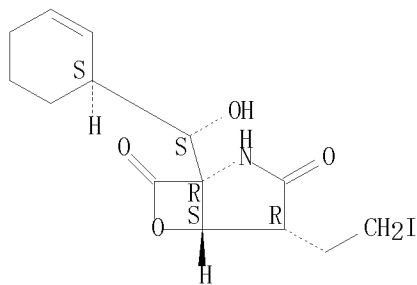
IT **855517-18-9P**

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic  
 preparation); THU (Therapeutic use); BIOL (Biological study); PREP  
 (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (structure-activity relationship studies of salinosporamide A  
 (NPI-0052), a novel marine derived proteasome inhibitor)

RN 855517-18-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



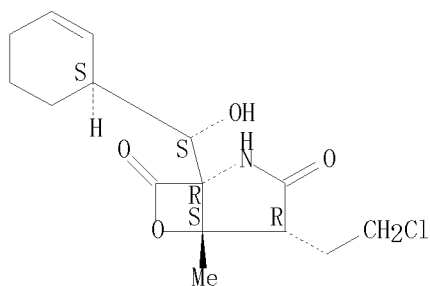
IT **437742-34-2**

RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use);  
 BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)  
 (structure-activity relationship studies of salinosporamide A  
 (NPI-0052), a novel marine derived proteasome inhibitor)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 855517-19-0P 855517-20-3P 855517-21-4P

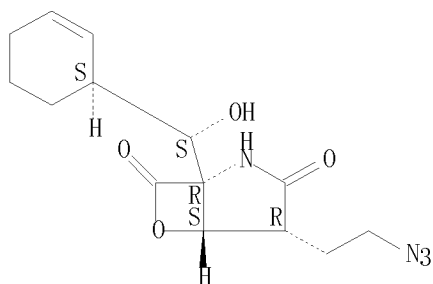
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(structure-activity relationship studies of salinosporamide A (NPI-0052), a novel marine derived proteasome inhibitor)

RN 855517-19-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-(2-azidoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-, (1R,4R,5S)- (CA INDEX NAME)

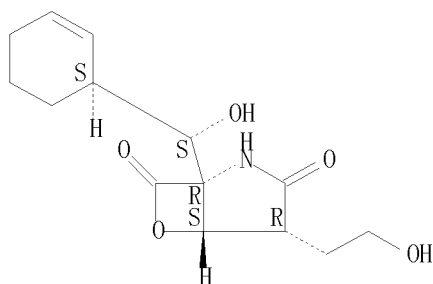
Absolute stereochemistry.



RN 855517-20-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

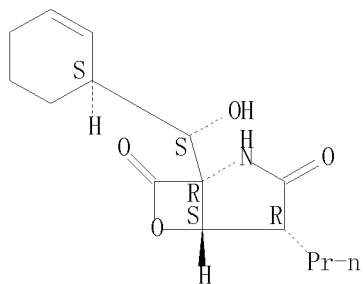


RN 855517-21-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-propyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.





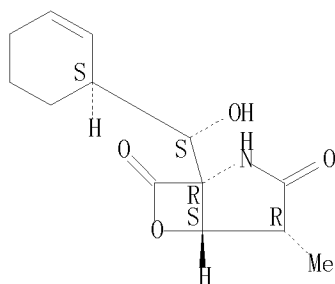
IT 855517-13-4      855517-14-5      855517-15-6  
855517-16-7      855517-17-8

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (structure-activity relationship studies of salinosporamide A  
 (NPI-0052), a novel marine derived proteasome inhibitor)

RN 855517-13-4 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-methyl-, (1R,4R,5S)- (CA  
 INDEX NAME)

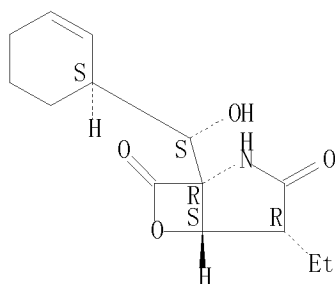
Absolute stereochemistry.



RN 855517-14-5 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-ethyl-, (1R,4R,5S)- (CA  
 INDEX NAME)

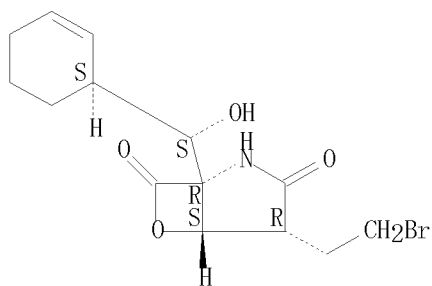
Absolute stereochemistry.



RN 855517-15-6 CAPLUS

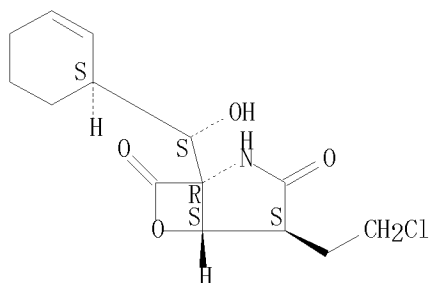
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-bromoethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-, (1R,4R,5S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



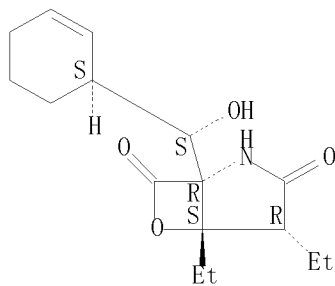
RN 855517-16-7 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-,  
 (1R, 4S, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



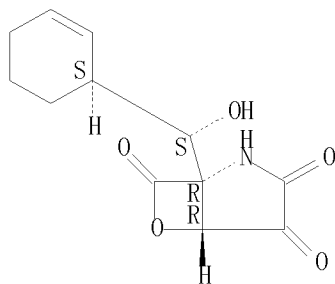
RN 855517-17-8 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-diethyl-, (1R, 4R, 5S)- (CA  
 INDEX NAME)

Absolute stereochemistry.



IT **855517-26-9P**  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (structure-activity relationship studies of salinosporamide A  
 (NPI-0052), a novel marine derived proteasome inhibitor)  
 RN 855517-26-9 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,4,7-trione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-, (1R, 5R)- (CA INDEX NAME)

Absolute stereochemistry.



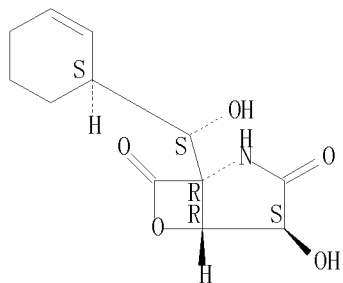
IT **855517-27-0P**

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (structure-activity relationship studies of salinosporamide A  
 (NPI-0052), a novel marine derived proteasome inhibitor)

RN 855517-27-0 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hydroxy-, (1R,4S,5R)- (CA  
 INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT:	105	THERE ARE 105 CAPLUS RECORDS THAT CITE THIS RECORD (105 CITINGS)
REFERENCE COUNT:	2	THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 161 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2005:29196 CAPLUS  
 DOCUMENT NUMBER: 142:107451  
 TITLE: Methods using [3.2.0]-heterocyclic compounds and  
 analogs thereof for the treatment of cancer, an  
 inflammatory condition, and/or an infectious disease  
 INVENTOR(S): Palladino, Michael; Neuteboom, Saskia Theodora  
 Cornelia; Macherla, Venkata Rami Reddy; Potts, Barbara  
 Christine  
 PATENT ASSIGNEE(S): Nereus Pharmaceuticals, Inc., USA  
 SOURCE: PCT Int. Appl., 184 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005002572	A2	20050113	WO 2004-US19543	20040618
WO 2005002572	A3	20050512		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2004253478	A1	20050113	AU 2004-253478	20040618
CA 2532066	A1	20050113	CA 2004-2532066	20040618
US 20050049294	A1	20050303	US 2004-871368	20040618
EP 1638552	A2	20060329	EP 2004-776757	20040618
EP 1638552	B1	20110302		
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK			
BR 2004011677	A	20060829	BR 2004-11677	20040618
CN 1838952	A	20060927	CN 2004-80023710	20040618
JP 2007523862	T	20070823	JP 2006-517404	20040618
NZ 544588	A	20100625	NZ 2004-544588	20040618
MX 2005013982	A	20060525	MX 2005-13982	20051220
ZA 2006000536	A	20070530	ZA 2006-536	20060119
US 20090182027	A1	20090716	US 2008-136688	20080610
PRIORITY APPLN. INFO.:			US 2003-480270P	P 20030620
			US 2004-566952P	P 20040430
			US 2004-871368	B1 20040618
			WO 2004-US19543	W 20040618

OTHER SOURCE(S): MARPAT 142:107451

#### ABSTRACT:

Methods are disclosed for treating cancer, inflammatory conditions, and/or infectious disease in an animal comprising administering a therapeutically effective amount of a heterocyclic compound. The animal is a mammal, preferably a human or a rodent. Production of compds. by fermentation and synthesis is described.

IT **437742-34-2P**, Salinosporamide A

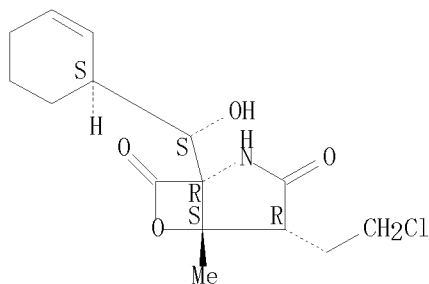
RL: BPN (Biosynthetic preparation); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); PUR (Purification or recovery); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(heterocyclic compds. and analogs for treatment of cancer, inflammation, and/or infectious disease)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **823229-30-7P** **823229-32-9P**

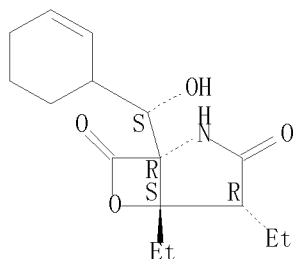
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PUR (Purification or recovery); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(heterocyclic compds. and analogs for treatment of cancer, inflammation, and/or infectious disease)

RN 823229-30-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-diethyl-, (1R,4R,5S)- (CA INDEX NAME)

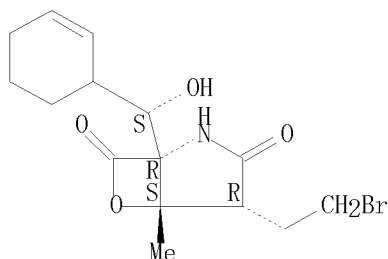
Absolute stereochemistry.



RN 823229-32-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-[(S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT **823229-26-1P** **823229-28-3P**

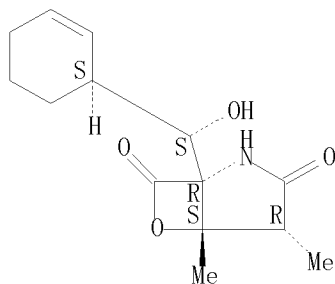
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(heterocyclic compds. and analogs for treatment of cancer, inflammation, and/or infectious disease)

RN 823229-26-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4,5-dimethyl-, (1R,4R,5S)-  
(CA INDEX NAME)

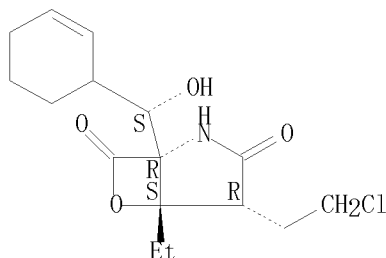
Absolute stereochemistry.



RN 823229-28-3 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-2-cyclohexen-1-ylhydroxymethyl]-5-ethyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



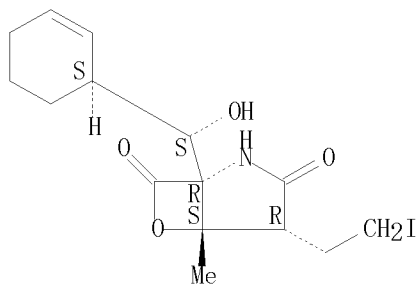
IT **823229-34-1P** **823229-48-7P**

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(heterocyclic compds. and analogs for treatment of cancer, inflammation, and/or infectious disease)

RN 823229-34-1 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-iodoethyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

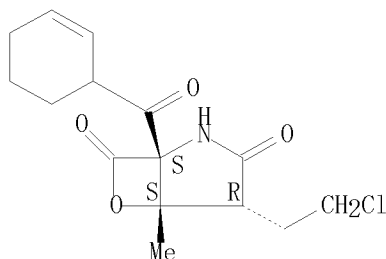
Absolute stereochemistry.



RN 823229-48-7 CAPLUS

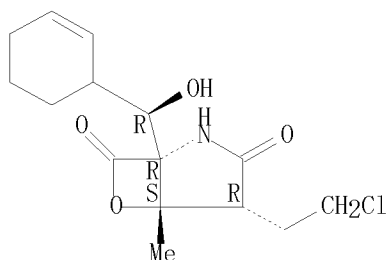
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-(2-cyclohexen-1-ylcarbonyl)-5-methyl-, (1S,4R,5S)-  
(CA INDEX NAME)

Absolute stereochemistry.



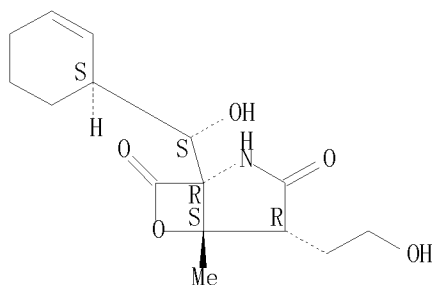
IT 823229-52-3P 823229-54-5P 823229-56-7P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (heterocyclic compds. and analogs for treatment of cancer, inflammation, and/or infectious disease)  
 RN 823229-52-3 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(R)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry.



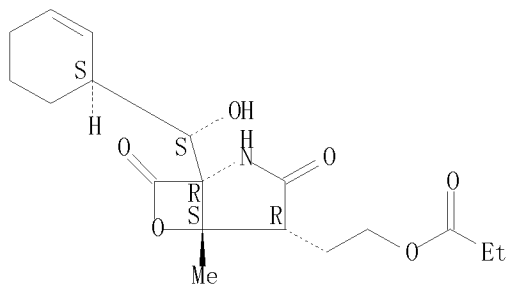
RN 823229-54-5 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(2-hydroxyethyl)-5-methyl-,  
 (1R, 4R, 5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

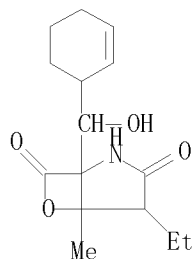


RN 823229-56-7 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-4-[2-(1-oxopropoxy)ethyl]-, (1R, 4R, 5S)- (CA INDEX NAME)

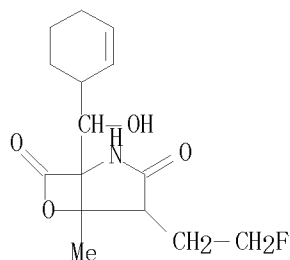
Absolute stereochemistry.



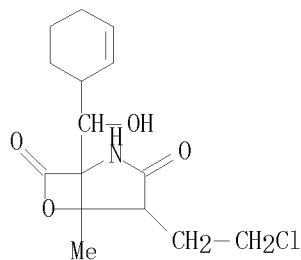
IT 823229-06-7      823229-08-9      823229-10-3  
823229-12-5      823229-14-7  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (heterocyclic compds. and analogs for treatment of cancer,  
 inflammation, and/or infectious disease)  
 RN 823229-06-7 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-(2-cyclohexen-1-ylhydroxymethyl)-4-ethyl-5-methyl- (CA INDEX NAME)



RN 823229-08-9 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 1-(2-cyclohexen-1-ylhydroxymethyl)-4-(2-fluoroethyl)-5-methyl- (CA INDEX  
 NAME)

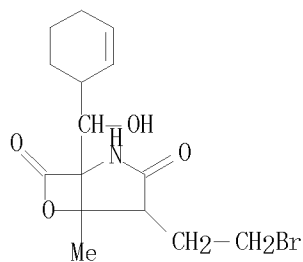


RN 823229-10-3 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-(2-cyclohexen-1-ylhydroxymethyl)-5-methyl- (CA INDEX  
 NAME)

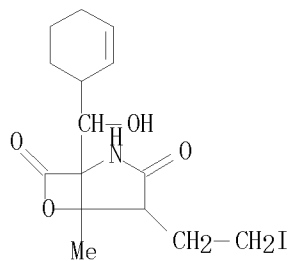




RN 823229-12-5 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-bromoethyl)-1-(2-cyclohexen-1-ylhydroxymethyl)-5-methyl- (CA INDEX  
NAME)



RN 823229-14-7 CAPLUS  
CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-(2-cyclohexen-1-ylhydroxymethyl)-4-(2-iodoethyl)-5-methyl- (CA INDEX  
NAME)



OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS  
RECORD (16 CITINGS)  
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 162 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2004:1127086 CAPLUS  
 DOCUMENT NUMBER: 142:54864  
 TITLE: Salinosporamides and methods for use thereof  
 INVENTOR(S): Fenical, William; Jensen, Paul; Mincer, Tracy; Feling, Robert H. R.  
 PATENT ASSIGNEE(S): The Regents of the University of California, USA  
 SOURCE: U.S. Pat. Appl. Publ., 30 pp., Cont.-in-part of U.S. Ser. No. 600,854.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040259856	A1	20041223	US 2004-838157	20040430
US 7176232	B2	20070213		
US 20040138196	A1	20040715	US 2003-600854	20030620
US 7179834	B2	20070220		
AU 2004253879	A1	20050113	AU 2004-253879	20040618
CA 2530215	A1	20050113	CA 2004-2530215	20040618
WO 2005003137	A1	20050113	WO 2004-US19453	20040618
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1638977	A1	20060329	EP 2004-776728	20040618
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
BR 2004011715	A	20060808	BR 2004-11715	20040618
CN 1823070	A	20060823	CN 2004-80020530	20040618
JP 2007523859	T	20070823	JP 2006-517371	20040618
NZ 544858	A	20090731	NZ 2004-544858	20040618
CN 101791306	A	20100804	CN 2010-10145487	20040618
US 20050239866	A1	20051027	US 2005-147622	20050607
US 7176233	B2	20070213		
MX 2005013985	A	20060317	MX 2005-13985	20051220
US 20070155815	A1	20070705	US 2007-705694	20070212
US 7635712	B2	20091222		
US 20090318529	A1	20091224	US 2009-561711	20090911
US 20100144826	A1	20100610	US 2009-638860	20091215
PRIORITY APPLN. INFO.:			US 2002-391314P	P 20020624
			US 2003-600854	A2 20030620
			US 2004-838157	A 20040430
			CN 2004-80020530	A3 20040618
			WO 2004-US19453	W 20040618
			US 2005-147622	A1 20050607
			US 2007-705694	A1 20070212

# ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 142:54864

## ABSTRACT:

The present invention is based on the discovery that certain fermentation products of the marine actinomycete strains CNB392 and CNB476 are effective inhibitors of hyperproliferative mammalian cells. The CNB392 and CNB476 strains lie within the family Micromonosporaceae, and the generic epithet Salinospora has been proposed for this obligate marine group. The reaction products produced by this strain are classified as salinosporamides, and are particularly advantageous in treating neoplastic disorders due to their low mol. weight, low IC<sub>50</sub> values, high pharmaceutical potency, and selectivity for cancer cells over fungi.

IT 437742-34-2P, Salinosporamide A

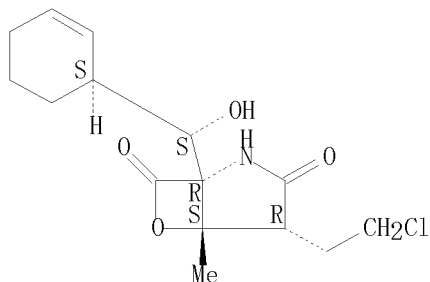
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BSU

(Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(anticancer salinosporamide)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT:	1	THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT:	65	THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 163 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2004:701941 CAPLUS  
 DOCUMENT NUMBER: 141:224070  
 TITLE: Preparation of  
 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione  
 (salinosporamide) derivatives for inhibition of  
 proteasomes and treatment of proteasome-mediated  
 diseases  
 INVENTOR(S): Stadler, Marc; Seip, Stephan; Mueller, Hartwig;  
 Mayer-Bartschmid, Anke; Bruening, Michael-Alexander;  
 Benet-Buchholz, Jordi; Togame, Hiroko; Dodo, Reiko;  
 Reinemer, Peter; Bacon, Kevin; Fuchikami, Kinji;  
 Matsukawa, Satoko; Urbahns, Klaus  
 PATENT ASSIGNEE(S): Bayer Healthcare AG, Germany; et al.  
 SOURCE: PCT Int. Appl., 79 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004071382	A2	20040826	WO 2004-EP1097	20040206
WO 2004071382	A3	20050106		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, RW, BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004212296	A1	20040826	AU 2004-212296	20040206
AU 2004212296	B2	20100617		
CA 2515940	A1	20040826	CA 2004-2515940	20040206
EP 1597262	A2	20051123	EP 2004-708731	20040206
EP 1597262	B1	20091111		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2004007234	A	20060131	BR 2004-7234	20040206
JP 2006517934	T	20060803	JP 2006-501755	20040206
CN 1845925	A	20061011	CN 2004-80009375	20040206
AT 448232	T	20091115	AT 2004-708731	20040206
ES 2336562	T3	20100414	ES 2004-708731	20040206
IN 2005DN03350	A	20070601	IN 2005-DN3350	20050727
IN 228043	A1	20090213		
MX 2005008478	A	20051018	MX 2005-8478	20050810
ZA 2005006367	A	20070131	ZA 2005-6367	20050810
US 20060229353	A1	20061012	US 2006-545449	20060327
US 20110015248	A1	20110120	US 2009-350696	20090108
PRIORITY APPLN. INFO. :			EP 2003-3495	A 20030214
			EP 2003-7594	A 20030402
			WO 2004-EP1097	A 20040206
			US 2006-545449	B3 20060327
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT				
OTHER SOURCE(S):		MARPAT 141:224070		
GRAPHIC IMAGE:				

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

#### ABSTRACT:

The title compound I and II [R1 = H, OH, methylcarbonyloxy; R2, R5 = cyclohexyl or cyclohexy-2-enyl, wherein cyclohexyl can be substituted with 0-2 hydroxy groups; R3, R6 = H or OH; R4 = H or OH; R7 = OH, cysteinyl, acetylaminoethylsulfanyl, methoxycarbonylethylsulfanyl, etc.] were prepared via fermentation of an Actinomycete of the genus Streptomyces and subsequently derivatized. Compds. I and II are useful as inhibitors of proteasomes for the treatment of proteasome-mediated diseases, such as asthma or cancer. For

example, compound III was isolated from the fermentation exts. and its structure was established by HPLC-MS and multi-dimensional NMR techniques. The latter showed an IC<sub>50</sub> =1 nM in the proteasome inhibition assay.

IT **744200-67-7P** **744200-68-8P**

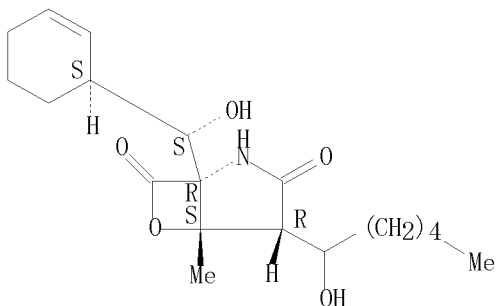
RL: PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(Preparation of 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione (salinosporamide) derivs. for inhibition of proteasomes and treatment of proteasome-mediated diseases)

RN 744200-67-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-(1-hydroxyhexyl)-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

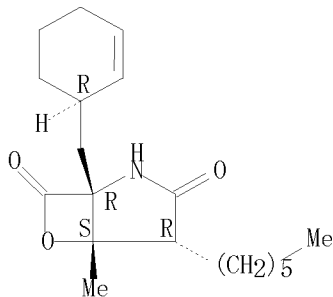
Absolute stereochemistry.



RN 744200-68-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(1R)-2-cyclohexen-1-ylmethyl]-4-hexyl-5-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **744200-75-7P**

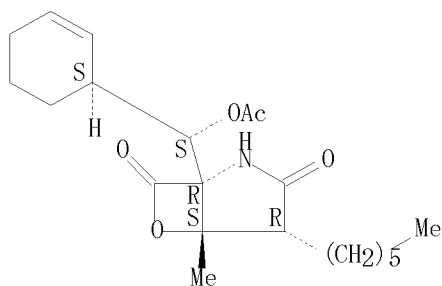
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(Preparation of 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione (salinosporamide) derivs. for inhibition of proteasomes and treatment of proteasome-mediated diseases)

RN 744200-75-7 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(acetyloxy) (1S)-2-cyclohexen-1-ylmethyl]-4-hexyl-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.

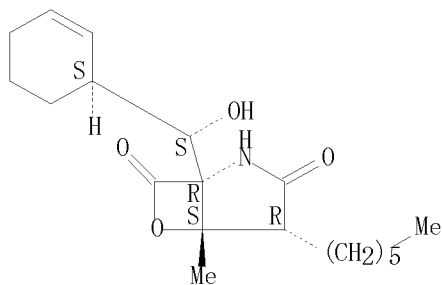
IT **744200-66-6P**

RL: PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(crystal structure; Preparation of 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione (salinosporamide) derivs. for inhibition of proteasomes and treatment of proteasome-mediated diseases)

RN 744200-66-6 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-4-hexyl-5-methyl-, (1R,4R,5S)-  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)

L6 ANSWER 164 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2004:570502 CAPLUS  
 DOCUMENT NUMBER: 141:105361  
 TITLE: Salinosporamides and methods for use thereof  
 INVENTOR(S): Fenical, William; Jensen, Paul; Mincer, Tracy; Feling, Robert H. R.  
 PATENT ASSIGNEE(S): The Regents of the University of California, USA  
 SOURCE: U.S. Pat. Appl. Publ., 26 pp.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040138196	A1	20040715	US 2003-600854	20030620
US 7179834	B2	20070220		
US 20040259856	A1	20041223	US 2004-838157	20040430
US 7176232	B2	20070213		
AU 2004253879	A1	20050113	AU 2004-253879	20040618
CA 2530215	A1	20050113	CA 2004-2530215	20040618
WO 2005003137	A1	20050113	WO 2004-US19453	20040618
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1638977	A1	20060329	EP 2004-776728	20040618
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
BR 2004011715	A	20060808	BR 2004-11715	20040618
CN 1823070	A	20060823	CN 2004-80020530	20040618
ZA 2006000473	A	20070425	ZA 2006-473	20040618
JP 2007523859	T	20070823	JP 2006-517371	20040618
NZ 544858	A	20090731	NZ 2004-544858	20040618
CN 101791306	A	20100804	CN 2010-10145487	20040618
US 20050239866	A1	20051027	US 2005-147622	20050607
US 7176233	B2	20070213		
MX 2005013985	A	20060317	MX 2005-13985	20051220
US 20070155815	A1	20070705	US 2007-705694	20070212
US 7635712	B2	20091222		
US 20090318529	A1	20091224	US 2009-561711	20090911
US 20100144826	A1	20100610	US 2009-638860	20091215
PRIORITY APPLN. INFO.:				
			US 2002-391314P	P 20020624
			US 2003-600854	A2 20030620
			US 2004-838157	A 20040430
			CN 2004-80020530	A3 20040618
			WO 2004-US19453	W 20040618
			US 2005-147622	A1 20050607
			US 2007-705694	A1 20070212

OTHER SOURCE(S): MARPAT 141:105361

#### ABSTRACT:

The present invention is based on the discovery that certain fermentation products of the marine actinomycete strains CNB392 and CNB476 are effective inhibitors of hyperproliferative mammalian cells. The CNB392 and CNB476 strains lie within the family Micromonosporaceae, and the generic epithet *Salinospora* has been proposed for this obligate marine group. The reaction products produced by this strain are classified as salinosporamides, and are particularly advantageous in treating neoplastic disorders due to their low mol. weight, low IC 50 values, high pharmaceutical potency, and selectivity for cancer cells over fungi.

IT 437742-34-2P, Salinosporamide A

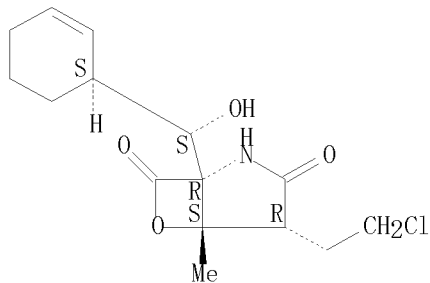
RL: BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)

(salinosporamides and anticancer use thereof)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

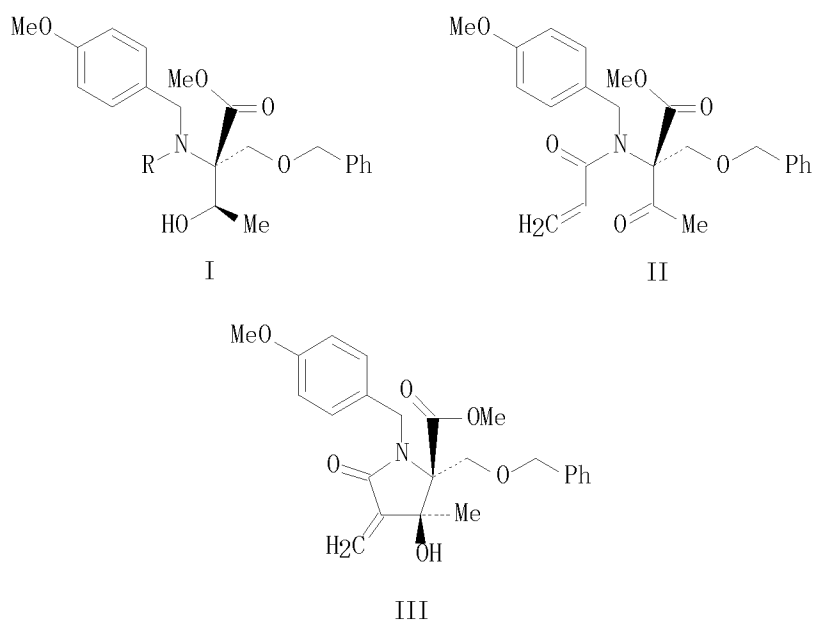


OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD  
(5 CITINGS)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L6 ANSWER 165 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2004:340603 CAPLUS  
 DOCUMENT NUMBER: 141:54117  
 TITLE: A Simple Stereocontrolled Synthesis of Salinosporamide A  
 AUTHOR(S): Reddy, Leleti Rajender; Saravanan, P.; Corey, E. J.  
 CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA, 02138, USA  
 SOURCE: Journal of the American Chemical Society (2004), 126(20), 6230-6231  
 CODEN: JACSAT; ISSN: 0002-7863  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 141:54117  
 GRAPHIC IMAGE:

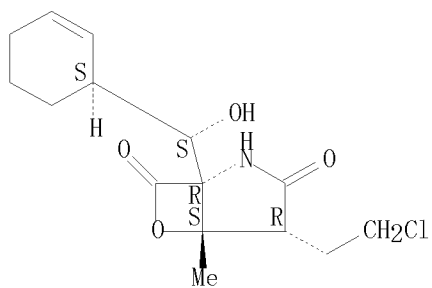


# ABSTRACT:

A simple and effective stereocontrolled synthesis of salinosporamide A has been developed. Of special note is the direct conversion of amino(benzyloxymethyl)hydroxybutanoate I (R = H) to acryloyl derivative I (R = COCH:CH<sub>2</sub>). Also, quinuclidine proved to be superior to other bases in the cyclization of oxybutanoate II to oxopyrrolidinecarboxylate III. This process, the first synthesis of salinosporamide A, is capable of providing the compound in substantial quantities for further biol. studies. Salinosporamide A was of special interest as a synthetic target because of its potent in vitro cytotoxic activity against many tumor cell lines (IC<sub>50</sub> values of 10 nM or less).

IT **437742-34-2P**, Salinosporamide A  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (asym. synthesis of salinosporamide A)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 112 THERE ARE 112 CAPLUS RECORDS THAT CITE THIS  
RECORD (114 CITINGS)  
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 166 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2003:101938 CAPLUS

DOCUMENT NUMBER: 139:81745

TITLE: Salinosporamide A: a highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus Salinospora

AUTHOR(S): Feling, Robert H.; Buchanan, Greg O.; Mincer, Tracy J.; Kauffman, Christopher A.; Jensen, Paul R.; Fenical, William

CORPORATE SOURCE: Center for Marine Biotechnology and Biomedicine  
Scripps Institution of Oceanography, University of California, La Jolla, CA, 92093-0204, USA

SOURCE: Angewandte Chemie, International Edition (2003), 42(3), 355-357

CODEN: ACIEF5; ISSN: 1433-7851

PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

A member of the "Salinospora" group was examined and was found that strain CNB-392 produces the chemical unique and highly bioactive metabolite salinosporamide A. Salinosporamide A exhibits potent cancer cell cytotoxicity and appears to exert its cytotoxic effects through inhibition of the 20S proteasome. "Salinospora" strain CNB-392 was isolated from a heat-treated marine sediment sample that was plated on sea-water-based agar nutrient medium. Salinosporamide A appears to be a direct product of the fermentation rather than a subsequent transformation product of a precursor similar in structure to that of lactacystin. Salinosporamide A displayed potent in vitro cytotoxicity against HCT-116 human colon carcinoma with an IC<sub>50</sub> value of 11 ng/mL. This compound also displayed potent and highly selective activity in the NCI's 60-cell-line panel with a mean GI<sub>50</sub> value (the concentration required to achieve 50% growth inhibition) of less than 10 nM and a greater than 4 log LC<sub>50</sub> differential between resistant and susceptible cell lines. The unique functionalization of the core bicyclic ring structure of salinosporamide A appears to have resulted in a mol. that is a significantly more potent proteasome inhibitor than omuralide.

IT **437742-34-2**, Salinosporamide A

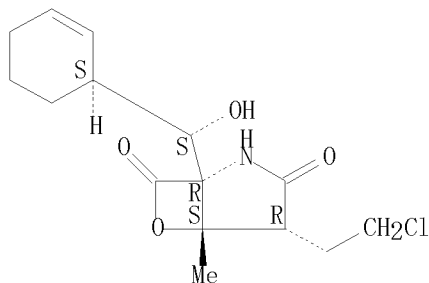
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(salinosporamide A: highly cytotoxic proteasome inhibitor from novel microbial source, marine bacterium of new genus Salinospora)

RN 437742-34-2 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
(1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 279 THERE ARE 279 CAPLUS RECORDS THAT CITE THIS RECORD (280 CITINGS)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 167 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 2002:465746 CAPLUS  
 DOCUMENT NUMBER: 137:43910  
 TITLE: Marine actinomycete taxon for drug and fermentation product discovery  
 INVENTOR(S): Fenical, William; Jenson, Paul R.; Mincer, Tracy J.  
 PATENT ASSIGNEE(S): The Regents of the University of California, USA  
 SOURCE: PCT Int. Appl., 30 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002047610	A2	20020620	WO 2001-US43758	20011116
WO 2002047610	A3	20021010		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2429163	A1	20020620	CA 2001-2429163	20011116
AU 2002043228	A	20020624	AU 2002-43228	20011116
US 20030157695	A1	20030821	US 2001-991518	20011116
US 7144723	B2	20061205		
EP 1341414	A2	20030910	EP 2001-989109	20011116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004535766	T	20041202	JP 2002-549186	20011116
JP 4395549	B2	20100113		
AU 2002243228	B2	20070802	AU 2002-243228	20011116
US 20060008852	A1	20060112	US 2005-228416	20050915
AU 2007203298	A1	20071011	AU 2007-203298	20070713
US 20080070273	A1	20080320	US 2007-841588	20070820
US 7879576	B2	20110201		
JP 2008119001	A	20080529	JP 2007-314720	20071205
US 20090069401	A1	20090312	US 2007-966787	20071228
US 20090197937	A1	20090806	US 2007-966801	20071228
PRIORITY APPLN. INFO.:			US 2000-249356P	P 20001116
			AU 2002-243228	A3 20011116
			JP 2002-549186	A3 20011116
			US 2001-991518	A1 20011116
			WO 2001-US43758	W 20011116
			US 2005-228416	A1 20050915
			US 2007-841588	A1 20070820

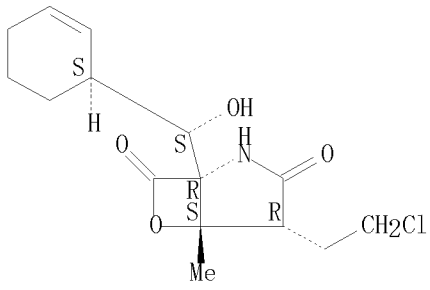
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

#### ABSTRACT:

The invention concerns the discovery of an actinomycete genus, given the name *Salinospora* gen. number, that displays an obligate requirement of the seawater (NA) for growth and unique 16S rRNA signature nucleotides. The invention is also the use of the genus for the production and discovery of active biomols. such as pharmaceutical agents, agrichems., immunomodifiers, enzymes and enzyme inhibitors.

IT **437742-34-2**, Salinosporamide A  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (marine actinomycete taxon for drug and fermentation product discovery)  
 RN 437742-34-2 CAPLUS  
 CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
 4-(2-chloroethyl)-1-[(S)-(1S)-2-cyclohexen-1-ylhydroxymethyl]-5-methyl-,  
 (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 7

THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD  
(9 CITINGS)

L6 ANSWER 168 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
ACCESSION NUMBER: 1999:178063 CAPLUS  
DOCUMENT NUMBER: 130:296964  
TITLE: The structural requirements for inhibition of  
proteasome function by the lactacystin-derived  
 $\beta$ -lactone and synthetic analogs  
AUTHOR(S): Corey, E. J.; Li, Wei-Dong Z.; Nagamitsu, Tohru;  
Fenteany, Gabriel  
CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Harvard  
University, Cambridge, MA, 02138, USA  
SOURCE: Tetrahedron (1999), 55(11), 3305-3316  
CODEN: TETRAB; ISSN: 0040-4020  
PUBLISHER: Elsevier Science Ltd.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

ABSTRACT:  
The synthesis of analogs of clasto-lactacystin  $\beta$ -lactone in which the  
substituents at C(5), C(7) and C(9) were systematically varied has led to a  
well defined structure-activity correlation for the highly selective inhibition  
of the mammalian 20 S proteasome.

IT 223246-07-9P

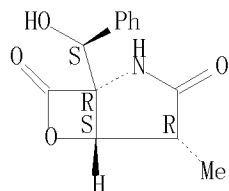
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); SPN (Synthetic preparation); BIOL (Biological  
study); PREP (Preparation)

(structural requirements for inhibition of proteasome function by  
lactacystin-derived  $\beta$ -lactone and synthetic analogs)

RN 223246-07-9 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione,  
1-[(S)-hydroxyphenylmethyl]-4-methyl-, (1R,4R,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 38 THERE ARE 38 CAPLUS RECORDS THAT CITE THIS  
RECORD (38 CITINGS)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 169 OF 169 CAPLUS COPYRIGHT 2011 ACS on STN  
 ACCESSION NUMBER: 1997:12301 CAPLUS  
 DOCUMENT NUMBER: 126:50959  
 ORIGINAL REFERENCE NO.: 126:9957a, 9960a  
 TITLE: Lactacystin analogs for inhibition of proteasomes and  
 treatment of proteasome-mediated diseases  
 INVENTOR(S): Schreiber, Stuart L.; Standaert, Robert F.; Fenteany,  
 Gabriel; Jamison, Timothy F.  
 PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA  
 SOURCE: PCT Int. Appl., 165 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9632105	A1	19961017	WO 1996-US5072	19960412
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
US 6335358	B1	20020101	US 1995-421583	19950412
US 5756764	A	19980526	US 1995-466468	19950606
US 6147223	A	20001114	US 1995-468408	19950606
IL 117887	A	20060820	IL 1996-117887	19960229
CA 2217817	A1	19961017	CA 1996-2217817	19960412
AU 9655423	A	19961030	AU 1996-55423	19960412
AU 705791	B2	19990603		
ZA 9602933	A	19970203	ZA 1996-2933	19960412
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1187769	A	19980715	CN 1996-194727	19960412
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PRIORITY APPLN. INFO.:			US 1995-421583	A1 19950412
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			US 1998-945092	A1 19980126
			US 2001-924993	A1 20010808

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 126:50959

#### ABSTRACT:

Compds. related to lactacystin and lactacystin  $\beta$ -lactone pharmaceutical compns. containing the compds., and methods of their preparation and use in treatment of proteasome-mediated diseases are claimed.

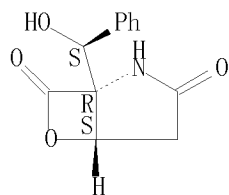
#### IT 183873-83-8P

RL: PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of lactacystin analogs for inhibition of proteasomes and treatment of proteasome-mediated diseases)

RN 183873-83-8 CAPLUS

CN 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 1-(hydroxyphenylmethyl)-, [1R-[1 $\alpha$ (S\*),5 $\alpha$ ]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT:	33	THERE ARE 33 CAPLUS RECORDS THAT CITE THIS RECORD (57 CITINGS)
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L3 276 SEA SSS FUL L1

D QUE L3 STAT

L4 272 SEA ABB=ON PLU=ON L3 AND CAPLUS/LC

L5 4 SEA ABB=ON PLU=ON L3 NOT L4

D 1-4 IDE CAN

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L6 169 SEA ABB=ON PLU=ON L3

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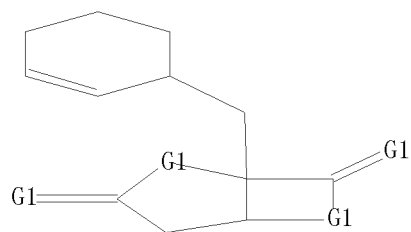
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